

EXHIBIT C11

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM
POWDER PRODUCTS MARKETING, SALES
PRACTICES AND PRODUCTS LIABILITY
LITIGATION**

MDL NO. 16-2738 (FLW) (LHG)

THIS DOCUMENT RELATES TO ALL CASES

**EXPERT REPORT OF BROOKE TAYLOR MOSSMAN, MS, PHD
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019



Brooke Taylor Mossman, M.S., Ph.D.

I. Scope Of Report

I was asked to address whether there is scientific evidence to support the theory that nonasbestos cleavage fragments present health risks to humans and the biological plausibility of plaintiffs' theory that cosmetic talc particles can migrate to the ovaries and cause cancer. I was also asked to review the experiments of Dr. Saed and the lab notebooks that were submitted by plaintiffs' counsel on his behalf and to comment on the opinions of Dr. Zelikoff. All the opinions in this report are stated to a reasonable degree of scientific certainty. I am being compensated at my customary rate of \$550.00 per hour for my work related to this litigation.

II. Summary Of Opinions

- Cosmetic talc particles and nonasbestos cleavage fragments are different chemically, physically and structurally from the amphibole asbestos types, crocidolite and amosite.
- Because of these different properties, cosmetic talc particles and nonasbestos cleavage fragments are unlikely to reach or be retained at sites of development of mesotheliomas or ovarian cancers.
- Talc and nonasbestos cleavage fragments are not reactive with cells, and effective repair pathways occur. Because they are distinct in chemistry and other features from asbestos fibers, they do not have the potential to cause the abnormal cell responses that are integral to the development of cancers.
- The trace amounts of cleavage fragments or other minerals that may be present in industrial or cosmetic talcs have little or no chemical or biological reactivity and do not play a role in critical cellular and molecular pathways leading to the development of mesotheliomas or ovarian cancers.
- The results of numerous epidemiologic and experimental studies assessing the carcinogenic (cancer causing) potential of short asbestos fibers (<5-10 microns in length) support the concept that short fibers and cleavage fragments, even of respirable dimensions, do not play a role in the induction of tumors.
- Experimental studies demonstrate no observed adverse effect levels from exposure to certain concentrations of asbestos fibers, indicating the existence of a threshold for cancer causation below which tumors do not occur.
- Gene expression studies show that mesothelial cells exhibit dose- and time-related changes in response to tumor-causing asbestos fibers, but not in response to talc. Ovarian epithelial cells are more resistant to gene changes by asbestos fibers and do not show inflammatory or cancer-related gene expression in response to talc.
- There is no scientifically plausible pathway of migration to the ovary or fallopian tubes by cosmetic talc particles, as would be required for talc to cause ovarian cancers.

- Dr. Saed's research does not in any way support or advance the theory that perineal talc use can cause ovarian cancer. His experimental design, methods and data are deeply flawed, he appears to have little to no knowledge about the origins of ovarian cancers, and he makes false analogies and speculative leaps in his report. His failure to disclose the source of his research funding for talc studies and sloppy, altered research notebooks further suggest that he conducted this research to advance litigation and not to advance scientific knowledge.
- Dr. Zelikoff's conclusions are not supported by peer-reviewed scientific papers in the literature or basic tenets of toxicology and carcinogenesis. She exhibits little understanding of the properties of talc or asbestos, and simply repeats other plaintiffs' experts' flawed theories of talc migration and inflammation. Portions of her report are copied from the Internet without citation or verbatim from other experts' reports, again without citation, highlighting the unscientific nature of her opinions. The lack of rigor in preparing her report and citations from legal documents would not be acceptable in the peer-reviewed scientific literature.

Each of my opinions is supported by my own research and scholarship in cancer research on asbestos for more than 40 years. I have organized and attended national and international scientific meetings on mechanisms of asbestos-related cancers and have served on key panels addressing cancer risks of minerals. I have also organized and participated in meetings between geologists and biologists seeking to understand the respective differences in minerals that might explain their different potencies in disease development. My opinions are also a product of my current review of the peer-reviewed scientific literature, editorial and reviewer activities, and participation on National Institutes of Health (NIH) study sections and scientific panels. I have had uninterrupted national research funding throughout my career. All of my research on asbestos fibers, talc and cleavage fragments has been published in peer-reviewed, high-impact scientific journals prior to the advent of my participation in talc litigation in 2014. In this report, I often reference reviews of my work and others in peer-reviewed papers and provide a glossary of scientific terms for clarification.

III. Background And Qualifications

My M.S. degree at the University of Vermont in 1970 was granted in human physiology, where I studied diagnostic methods for the detection of cervical cancers in the Department of Obstetrics and Gynecology in the Medical School. After moving to New York University, where I worked as a research assistant studying mechanisms of skin cancer, I returned to obtain my Ph.D. in Cell Biology from the University of Vermont in 1977 on mechanisms of asbestos-induced cancers. I am currently a Professor Emeritus and University Distinguished Professor of Pathology at the University of Vermont College of Medicine. I have been studying the roles of asbestos fibers in the induction of lung cancers, asbestosis, and mesotheliomas in the Department of Pathology at the University of Vermont College of Medicine for more than 40 years. Through research grant awards by several institutes of the NIH, Environmental Protection Agency (EPA) and American Cancer Society awarded to me throughout my career, I have elucidated the importance of inflammation-causing, genetic and cell signaling pathways by amphibole asbestos (with an emphasis on crocidolite) in the causation of lung cancers and mesotheliomas. Recent research

has focused on blocking these pathways in experimental studies to allow the development of therapeutic approaches for patients with mesothelioma. I have performed inhalation studies in rodents, studied the effects of asbestos types and other minerals (serpentine and amphibole cleavage fragments of asbestos, talc, etc.) on rodent and human ovarian epithelial and mesothelial cells, i.e., *in vitro* studies, and confirmed many of these observations in both human mesothelioma tissues and a model of peritoneal mesothelioma after injection of human mesothelioma cells into immunocompromised mice.

My fields of specialization include: environmental toxicology, mesothelial and epithelial cell differentiation, chemical and physical carcinogenesis and cell injury, pulmonary fibrosis, reactive oxygen species (ROS), molecular biology of antioxidant enzymes, and cell signaling pathways leading to inflammation and cancer. My scholarship has included a focus on asbestos-induced diseases, and I have made numerous and sustained contributions to the field of fiber carcinogenesis and the study of asbestos. My work serves as a foundation for significant amounts of research on asbestos-related diseases.

I have published more than 300 refereed papers, books, book chapters, reviews and monographs on my research in the scientific literature and have chaired and presented my research at more than 100 meetings and seminars on mechanisms of asbestos- and silica-related diseases. I have received numerous national and international meeting invitations to present my research, as well as awards for my research accomplishments that include the prestigious Wagner Award for historic contributions to mesothelioma research from the International Mesothelioma Interest Group, a Career Achievement Recognition Award for Scientific Accomplishments from the American Thoracic Society, appointment to the Board of Councilors of the National Cancer Institute, and election to the Plutocrat Society of the University Associates in Pathology.

At the University of Vermont, I have directed an Environmental Pathology training grant from the National Institute of Environmental Health Sciences (NIEHS) (1995-2013), have served as Director of the University's Environmental Pathology Program (1995-2013), and am a former Chair of the Cell and Molecular Biology Program (1984-88). In 2011, I received one of only 10 University Distinguished Professor Awards, awarded historically in recognition of outstanding contributions to my discipline. The award noted that my "scientific contributions over the past 30 years are numerous and sustained, resulting in international recognition as one of the world's foremost authorities in the field of fiber carcinogenesis." This is a lifetime award that allows me to maintain my University office and service activities. I have also won both Medical Scholar and Alumni Achievement Awards for "outstanding achievements in research, education, public service and humanitarianism" in the UVM College of Medicine, and I have recently been elected to the Vermont Academy of Arts and Sciences "as a leading researcher in asbestos-induced carcinogenesis."

I have served on numerous advisory boards at other universities as well as scientific advisory boards and study sections of the National Heart, Lung and Blood Institute (NHLBI), National Cancer Institute (NCI), American Cancer Society, NIEHS, and EPA. I was the first woman to chair the advisory board of the Lung Institute of NHLBI and have most recently served as Chair of grant review panels for this institute and others. I have also organized and chaired

international and national conferences featuring experts in the fields of mineralogy, asbestos and mesothelioma research. Through review of research grants and papers as part of my editorial services for a number of scientific journals, I keep up with contemporary developments in my field of research.

I was a reviewer of both the EPA strategic plan for studies on Libby amphibole as well as the “NIOSH Roadmap for Research on Asbestos Fibers and Other Elongate Mineral Particles” on behalf of the Institute of Medicine National Academies. I served on the founding board of the Center for Asbestos-Related Diseases (CARD) in Libby, Montana, where I was awarded a Focus Award for my dedication and voluntary contributions, and have just completed a voluntary term on the scientific advisory board of the Mesothelioma Applied Research Foundation (MARF). I am currently serving on the scientific review committee for the National Virtual Mesothelioma Bank, and am on the external advisory board for an NIH-funded Superfund grant on asbestos at the University of Pennsylvania. I have been invited recently to serve on the International Mineralogical Association working group panel “[t]o clarify issues associated with asbestos and other respirable minerals-nomenclature and classification” and was one of six invited speakers and session coordinators at a conference on “Asbestos in Talc” in November 2018 at The Joint Institute of Food Safety and Applied Nutrition (FDA). I am, or have been, a member of the American Society of Cell Biology, American Association for the Advancement of Science, Sigma Xi Scientific Honor Society, Oxygen Society, Tissue Culture Association, American Association for Cancer Research, International Association for the Study of Lung Cancer, American Thoracic Society, and the American Society of Investigative Pathology. I serve on the editorial board or as a reviewer for: *Journal of Cellular Physiology*, *Environmental Research*, *Cell Biology & Toxicology*, *In Vitro Toxicology*, *Cancer Research*, *Experimental Cell Research*, *Experimental Lung Research*, *Scanning Electron Microscopy*, *American Journal of Pathology*, *Science*, *American Industrial Hygiene Association Journal*, *European Journal of Cancer & Clinical Oncology*, *Journal of Toxicology and Applied Pharmacology*, *Environmental Mutagenesis*, *Carcinogenesis*, *American Review of Respiratory Diseases*, *Journal of the American College of Toxicology*, *Journal of the National Cancer Institute*, *Nature*, *Journal of Leukocyte Biology*, *New England Journal of Medicine*, *Cell & Tissue Kinetics*, *Clinical Pathology and Pharmacology*, *American Journal of Respiratory Cell and Molecular Biology*, *Risk Analysis*, *Clays and Clay Minerals*, *Chest*, *Chemical Research in Toxicology*, *Atherosclerosis*, *Journal of Clinical and Laboratory Medicine*, *New Journal of Chemistry*, *Drug and Chemical Toxicology* (past section Head of In Vitro Toxicology), *Particle and Fibre Toxicology*, *PLOS*, *Cancer Letters*, *Oncotarget*, and *Archives of Biochemistry & Biophysics*.

My roles as an editor and reviewer of many scientific journals for decades have made me aware of the importance of disclosures and rigor in reviewing that were ignored in submissions of Dr. Saed’s recent abstracts and paper.

These many tasks have also led to formulation of my scientific opinions as outlined above.

My prior deposition and trial testimony for the last four years is listed in **Exhibit A**, references cited within my report, including those supporting my opinions, are listed in **Exhibit B**, and a copy of my complete *Curriculum Vitae* is attached as **Exhibit C**.

IV. Scientific Methodology And The Importance Of The Scientific Peer Review Process

Publishing one's research findings in the peer-reviewed scientific literature is fundamental to the academic review process, promotion and tenure at research institutions world-wide. Moreover, it is a requirement to obtain funding from the NIH and other funding agencies. Scientific journals are ranked according to their impact factors: the higher the factor, the more prestigious the journal. When applying for promotion or tenure, faculty members often present their publications in terms of impact factors to obtain a score high enough for consideration at their respective institutions.

When submitting peer-reviewed papers, a journal is selected, the paper is uploaded to that website, and an Editor or member of the Editorial Board sends the paper for review to colleagues in the field for comments, acceptance or disapproval. The higher the impact factor, the more stringent the review process. Reviewers for high-impact journals are generally not disclosed to the investigator submitting the paper and may suggest major or minor revisions before acceptance of the research for publication. In general, reviewers are asked to judge: 1) the significance of the study; 2) the appropriateness of the scientific methods used, including the numbers of samples, numbers of repeated experiments and necessary controls; 3) the methods for statistical analyses of data; and 4) the interpretation of data. Disclosure of conflicts of interest, i.e. whether or not the authors may have a financial or other bias in supporting or reporting their research results, and acknowledgements of research funding support, are required by almost all journals. After receiving reviews of one's submitted paper, the first listed or senior author can respond in a point-by-point fashion to suggested revisions or the need for additional experiments. These revisions are passed on to the original reviewers, who are asked to communicate their recommendations to the Editor and authors. The peer-review process for most journals may take several months, depending on needed additions and editorial decisions.

Table 1 shows impact factors for several journals in the scientific literature.

Table 1. Impact factors for scientific journals

Journal:	Impact Factor:
<i>New England J. of Medicine</i>	79.260
<i>Science</i>	41.058
<i>Proceedings of the National Academy of Sciences</i>	9.504
<i>Cancer Research</i>	9.130
<i>Particle and Fibre Toxicology</i>	6.105
<i>Gynecologic Oncology</i>	4.540
<i>American J. Respiratory Cell & Molecular Biology</i>	3.785
<i>Reproductive Sciences</i>	2.548
(Science Citation Index, 2017)	

In contrast to peer-reviewed scientific publications, other publications such as abstracts, book chapters, case reports, Updates or Reviews, Letters to the Editor, and Commentaries are generally not formally reviewed by peers in the scientific community before publication. Hence, scientific inaccuracies and flaws in interpretation of data can occur.

In addition to publishing in the peer-reviewed scientific literature, it is important to participate on interdisciplinary scientific panels that address important health and regulatory questions. In the field of asbestos-induced diseases, I have served on panels for months and years with toxicologists from industry, academia and government, geologists, biostatisticians, clinicians, dosimetry experts, pathologists and molecular biologists to gain an appreciation of how asbestos minerals cause disease.

V. Principles Of Toxicology: Epidemiology, Animal And *In Vitro* Experiments

“Toxicology” is broadly defined as the study of any agent that causes adverse changes in cells of the body. There are many manifestations of toxicity or injury to cells that occur when normal defense mechanisms are overwhelmed. As emphasized by Drummond et al. (2016), the toxicity of inhaled fibers such as asbestos is described by a **3D** paradigm that recognizes the importance of **Dose, Dimensions** (long fiber length and fine/narrow diameter) and **Durability** in cancer development by minerals. These fundamental tenets of toxicology and cancer development have been endorsed by many panels of scientists evaluating risks of asbestos fibers (e.g., IARC, 1989; IARC, 2012; NAS, 1984; NRC, 2006; Health Effects Institute, 1991; ATSDR, 2003; Institute of Medicine, 2009).

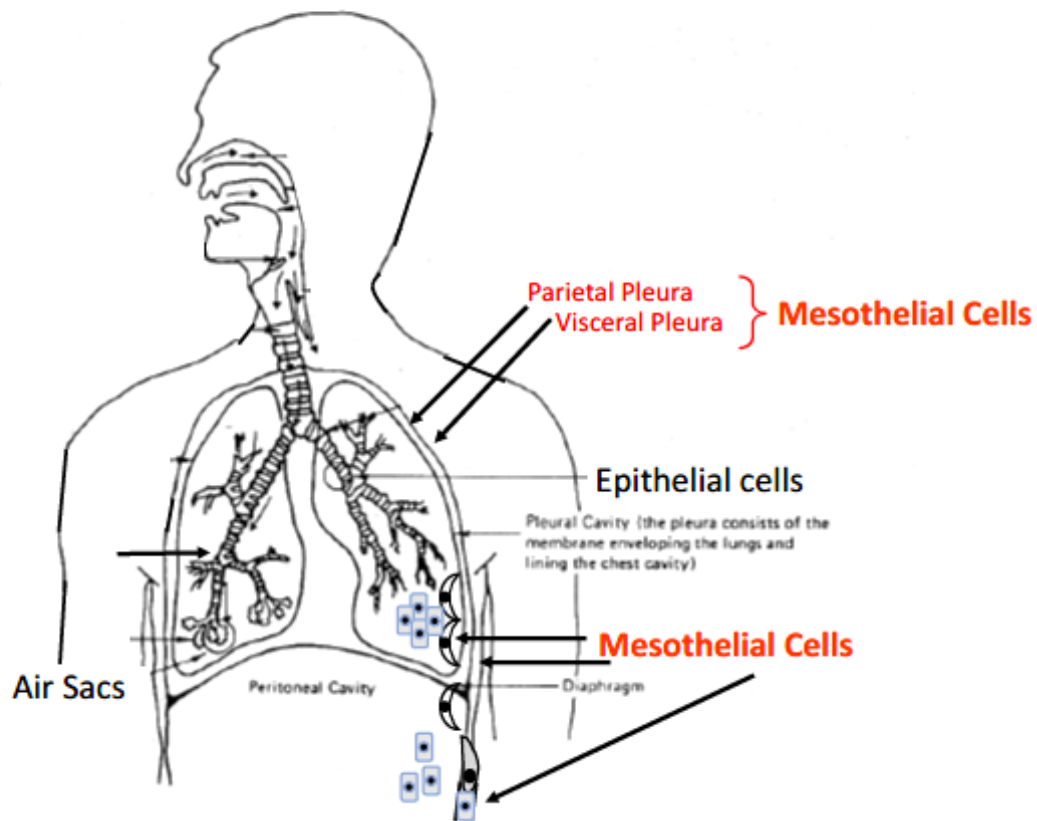
“Epidemiology,” the study of human populations, is often fundamental to assessing the health risks of minerals in occupational settings. However, because workers may be exposed to different types of minerals occupationally and environmentally and have a number of mineral types in their lungs, emphasis historically has been placed on results of studies in animals, i.e., *in vivo* experiments, where exposures to one mineral type can be assessed. As summarized by Drummond et al. (2016), an extensive database exists in rodents after inhalation, intratracheal instillation and intracavity injections of minerals (into the pleural or peritoneal cavities). Although inhalation experiments are the “gold standard” because they represent the natural route of exposure to inhaled particles, all methods are useful. For example, false positives (minerals that cause tumors in animals but not humans) may occur using intraperitoneal injections, but negative results exonerate a mineral from classification as a carcinogen (Drummond et al., 2016). This statement is of central importance to interpreting animal data on talc or cleavage fragments (see below).

In vitro experiments in which cell cultures and tissues (organ cultures) are kept outside of the body are also important models in toxicology. Exposures to defined concentrations and types of minerals can be examined in efforts to understand mechanisms of cancer causation and/or cell defense. It is important to use positive (known cancer-causing agents) and negative (non-cancer-causing agents) controls in these experiments when postulating mechanisms linked to cancer development. For example, any particle or fiber can be toxic to cells at very high concentrations due to mechanical injury.

VI. Anatomy Of The Lungs And Pleura

An understanding of the architecture of the human lung is necessary to determine how lungs respond to inhaled materials. As diagrammed in **Figure 1**, inhaled particles enter through nasal passages. Some are swallowed, but the majority enter the airways through the tracheal tube that then branches into a series of progressively smaller airways (bronchioles). These tubes connect to the air sacs (alveoli) of the lung, where gases such as oxygen and carbon dioxide are exchanged.

Figure 1. Diagram illustrating cell types of the human lung and pleura.



The cells that line the trachea (main upper air tube), bronchioles and air sacs are called “epithelial cells” and can give rise to lung cancers, but primarily serve to protect the lung from foreign matter or allow gas exchange. These cells are supported by a matrix composed of cells called “fibroblasts” that can also thicken or multiply to give rise to the many forms of pulmonary fibrosis. This nonmalignant disease can be progressive and lethal in patients exposed to high (occupational) concentrations of asbestos, i.e., asbestosis. In contrast, talcosis, or fibrosis of the lungs, as demonstrated in some talc miners and millers, is different in its clinical features and pathology (Guthrie and Mossman, 1993 (*see* chapter by Kane)). It is **not** a malignant disease.

The pleural cavity consists of fluids around the lung and cells of the immune system that may accumulate in response to infection or foreign material. “Mesothelial cells” that line the lung are called visceral pleural mesothelial cells, and mesothelial cells that make up the outside sac enclosing the lungs are called parietal pleural mesothelial cells (see **Figure 1**). These cell types make mesothelial fluids that allow the lung to expand and contract during normal respiration. Mesothelial cells also line the peritoneal and pericardial cavities. Mesothelial cells give rise to mesotheliomas after exposures to certain amphibole asbestos types, radiation, and other asbestos-like minerals such as erionite and fluoro-edenite, but approximately 20% of patients with mesothelioma have no known exposures to these agents, and tumors may arise spontaneously or by genetic predisposition (Ilgren and Wagner, 1991; Sherwood et al., 2008; Testa et al., 2011).

A. Inhalation and translocation of particles and fibers

The diameter of particles governs whether they are inhaled and how deep in the lung they can penetrate (reviewed in Mossman et al., 2011). For example, fibers greater than 3 microns in diameter do not generally get inhaled, fibers > 1.5 microns in diameter do not penetrate the deep lung, and fibers > 0.5 microns in diameter do not get out to the pleura that line the lung (Lentz et al., 2003; McClellan et al., 1992).

B. Natural defense mechanisms: How the lungs dispose of foreign particles (roles of macrophages and the lymphatics)

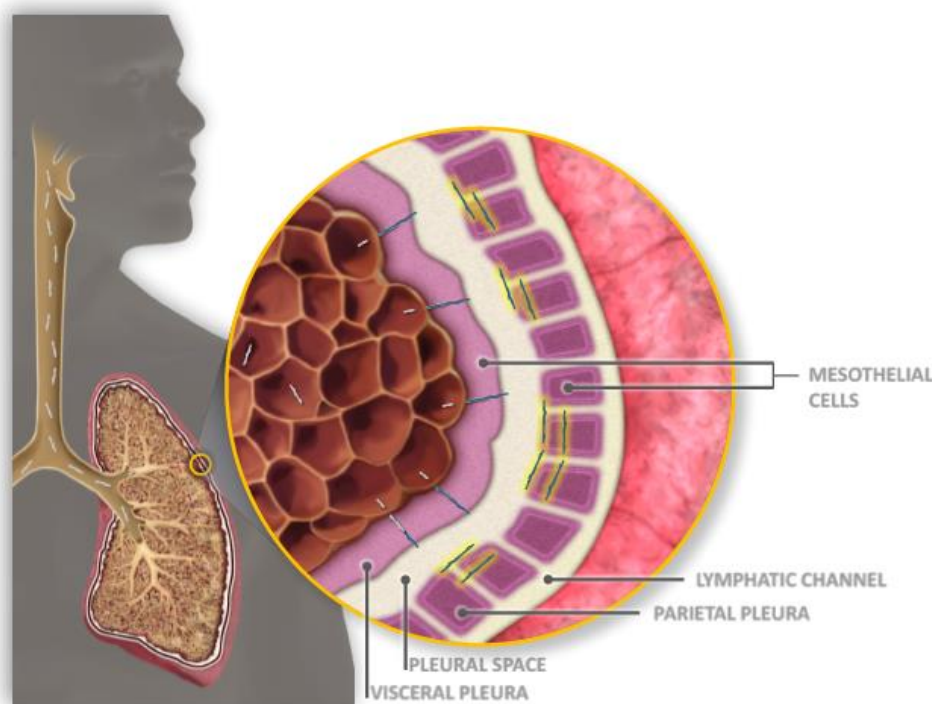
Cells called “macrophages” occur throughout the body, and populations of these cell types within the lung and pleura are called “alveolar” and “pleural” macrophages, respectively. These cell types arise from the bone marrow and can also multiply or change in function at sites of deposition of particles or microorganisms, processes linked to lung repair. The normal function of macrophages is to clear particles from the lung after they engulf them, a process known as “phagocytosis.” Particles or fibers that are effectively taken up by macrophages are cleared from the lungs as these cells move up the airways or enter the lymphatic system (see below). Many macrophages are propelled up and out of the lung by mucin secretions and hair-like cells called ciliated epithelial cells, often referred to as the mucociliary escalator. Other macrophages remain at sites of particle deposition and signal other cell types of the immune system, called “neutrophils” or “lymphocytes,” to accumulate and acquire immunity to combat toxic agents. The secretion of proteins called “cytokines” that signal to other cells of the immune system and cause these and other cell types in the area to proliferate or divide is a natural defense mechanism. However, many cytokines can also favor disease development if secreted in large amounts.

The lymphatic system consists of the lymph nodes and spleen, together with masses of lymphoid tissues in the respiratory tract and intestinal mucosa. The primary function of the lymphatic system is to provide immunologic defenses against foreign material. The lymph nodes serve as deposits for agents, and they are interconnected by lymphatic channels. “As the lymph fluids flow through the nodes, the phagocytic cells filter out and destroy any microorganisms that have gotten into the lymphatic channels” (Crowley, 2001). The lymphocytes (white blood cells within the node and elsewhere in the body) and macrophages also interact with the foreign material to

initiate an immune response. In the general population, many particles and fibers are found in lymph nodes throughout the body (Dodson et al., 2000).

Long, thin asbestos fibers can align themselves with airways and penetrate the deep lung to get to the pleura. Because of their large size, they are not effectively removed by normal clearance mechanisms, including alveolar macrophages, which cannot engulf or remove long fibers. At low concentrations, long fibers may pass through stomata to lymphatic channels for elimination. Stomata are channels approximately 10 microns in diameter that exist between mesothelial cells. At high concentrations of fibers, a bottleneck-like phenomenon occurs, whereby these channels are blocked, and fibers remain at sites of tumor development (Moalli et al. 1987; Murphy et al., 2011). In contrast, smaller fragments of minerals may drain out through the lymphatic system (see **Figure 2**).

Figure 2. Diagram showing how long thin asbestos fibers become lodged at the pleural surface.



C. Inflammation and repair (oxidants and antioxidants)

The body has effective defense mechanisms for dealing with microorganisms and other potentially harmful substances. One mechanism is inflammation, “a nonspecific response to any harmful agent and includes phagocytosis of the material by neutrophils and macrophages” (Crowley, 2001). A first line of defense in inflammation is accumulation of macrophages and other cell types of the immune system in an orchestrated response to remove foreign materials. Importantly, we and others have characterized the inflammatory response in the lungs and pleura after inhalation of asbestos fibers and other materials and have shown that phagocytosis (i.e., cell uptake of these particles) results in intracellular and extracellular release of oxidants, often called reactive oxygen species (ROS) or reactive nitrogen species (RNS). Oxidants can interact with the DNA, lipids and proteins in cells to cause abnormal cell function.

We have characterized repair mechanisms in response to minerals, including a number of intracellular enzymes and proteins that are called “antioxidants” (Mossman et al., 1986; Shatos et al., 1997; Mossman et al., 1990; Janssen et al., 1990; Shull et al., 1991; Janssen et al., 1992; Holley et al., 1992; Janssen et al., 1993; Janssen et al., 1994; Mossman et al., 1996; Shukla et al., 2003; Mossman et al., 2011). At low exposure levels to minerals, antioxidants scavenge damaging oxidants, and effective repair is observed. However, at high concentrations of minerals, normal defense mechanisms can be overwhelmed. Dimensions and chemistry (i.e., iron content, availability and charge) are some of the factors driving production of oxidants (reviewed by Shukla et al., 2003).

D. Chronic inflammation and foreign body carcinogenesis

Chronic irritation and inflammation by cigarette smoke, asbestos and silica have been linked to the development of lung cancers (Kamp et al., 2011; Rakoff-Nahoum, 2006; Balkwill and Mantovani, 2002; Coussens and Werb, 2002). However, there is also evidence suggesting that inflammation and immune system stimulation inhibit the development of other cancers. Reviews on the topic emphasize that acute inflammation “is a beneficial response activated to restore tissue injury and pathogenic agents” (Landskron et al., 2014). Chronic inflammation over months and years can result in many diseases, including cancers, but has not been established as a cause of ovarian cancer – and there is evidence that is difficult to reconcile with the inflammation hypothesis (Ni et al., 2012). Notably, Rakoff-Nahoum (2006) cautions, “[t]he relationship between cancer and inflammation is not simple and cannot be reduced to one grand theory.”

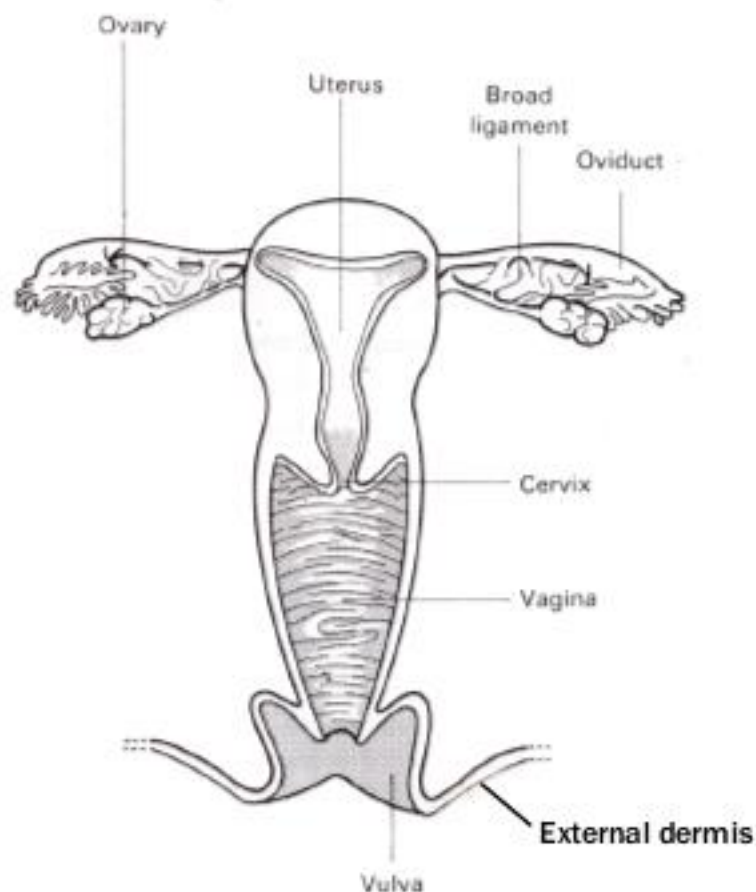
We and others proposed that long, durable asbestos fibers in lungs and pleura served as “foreign bodies” in tumor development by acting as stimuli for frustrated cell uptake and continual release of oxidants (reviewed in Shukla et al., 2003; Kamp et al., 2011). We have also shown that oxidant release by high iron-containing crocidolite or amosite asbestos triggers abnormal cell responses and signaling pathways intrinsic to tumor development (reviewed in Mossman et al., 2011; Mossman et al., 2013). Moreover, we have prevented crocidolite asbestos-induced inflammation and hallmarks of disease development in both animals and *in vitro* models after administration of antioxidants (Mossman et al., 1986; Shatos et al., 1987; Mossman et al., 1990; Mossman et al., 1996).

VII. Anatomy Of The Female Reproductive Tract And Barriers To Particles

Protective surface mechanisms, tissue defenses including inflammation, and immune responses cooperate in protection of the female reproductive tract from disease-producing foreign matter. As illustrated in **Figure 3** below, the external genitalia are a first line of defense in that “the skin constitutes a relatively impenetrable barrier to most micro-organisms unless breached by injury such as abrasion or burning” (Burkitt et al., 1993, p. 191). The opening of the vagina is also enclosed by thick layers of skin (labia). Both muscular tissue and mucous layers similar to the mucociliary escalator of the respiratory tract line the vagina, uterus, and oviducts, and are protective against foreign matter.

Ovarian cancers develop from epithelial cells that line the ovaries and oviducts (Fallopian tubes). These structures are surrounded by a protective fibrous capsule. Ovarian epithelial cells are distinct from endometrial epithelial cells that line the uterus and give rise to endometrial cancers. Based upon these barriers, it is difficult to conceive of a route whereby talc, either after perineal dusting or inhalation, would reach and persist in epithelial cells in sufficient doses to cause ovarian cancers.

Figure 3. Diagram of the female reproductive system (modified from Burkitt et. al., 1993).



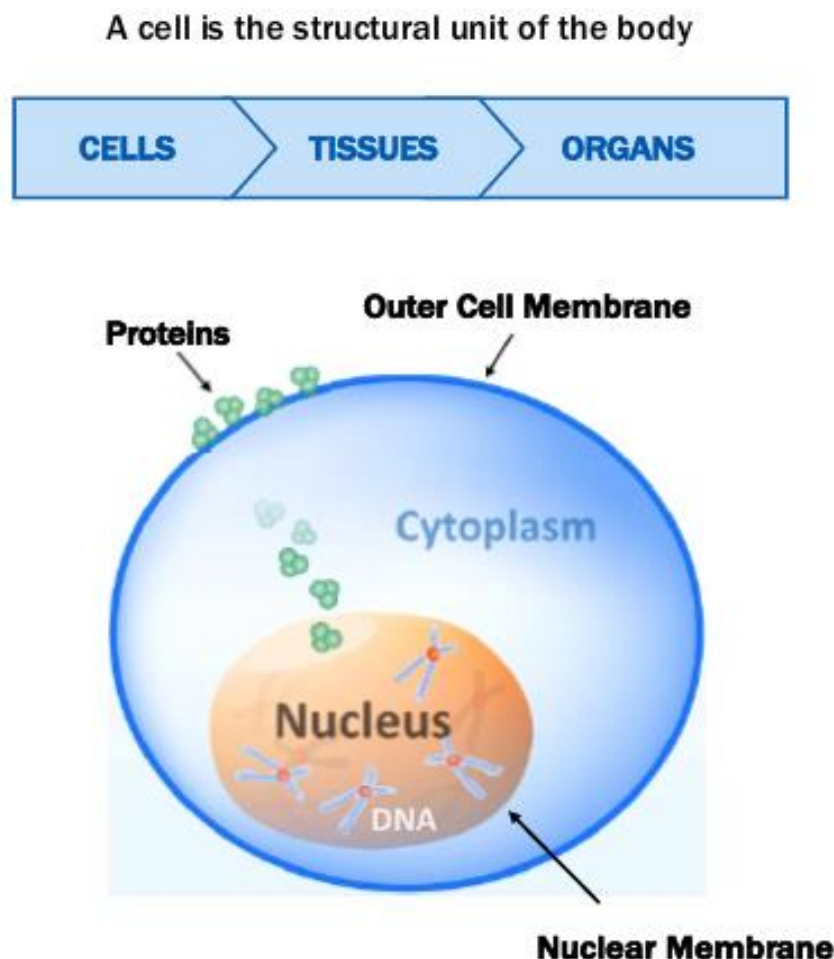
VIII. Cancer Development

A. What is a normal cell and how is a cancer cell altered?

The human body has billions of cells that serve a number of roles in maintaining the function of the human body, i.e., normal physiology. The cell is the building block of tissues and organs, and where cancers begin. Since changes in normal cell function can result in cancers, it is important to understand the fundamental structures of the cell and how they are altered in cancer. **Figure 4** is a diagram of a cell that illustrates the various organelles, i.e., intracellular structures important

in normal cell function. The cell is surrounded by an external membrane that encloses the two main compartments of the cell: 1) the nucleus, which contains the genetic material or DNA that is packaged into genes, and 2) the cytoplasm, in which organelles controlling cell respiration and other functions occur. Historically, scientists have focused on the DNA in the nucleus and how it is processed through the formation of RNAs to proteins that give rise to abnormal cell function. It is recognized that both genetic alterations to DNA and epigenetic changes (i.e., those that do not affect the DNA structure) are important in cancer development. **Figure 4** also shows proteins comprising receptors on the external cell membrane and occurring in cascades within the cells that are the focus of most current cancer research because they are altered in cancer development.

Figure 4. Diagram of the components of the cell.



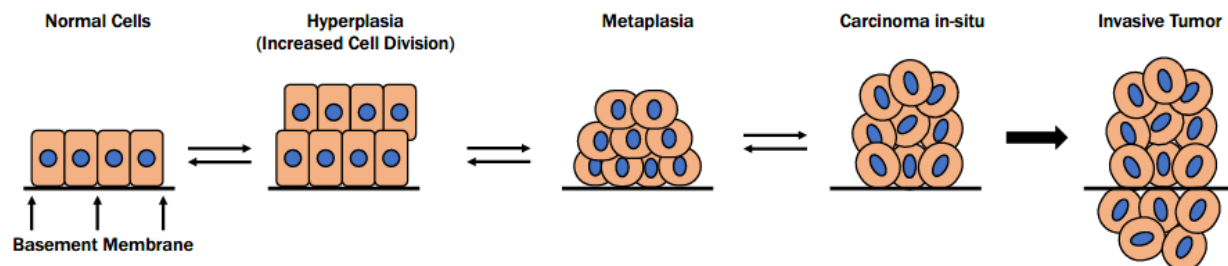
B. Stages of cancer development

Cancer is “a disease of abnormal gene expression” characterized by uncontrolled cell proliferation or division and abnormal differentiation, i.e., altered cell function (Coleman and

Tsongalis, 2017). Consistent with epidemiologic studies showing that asbestos-associated cancers of the lung and pleura develop over many decades, examination of animal tissues and cells exposed to asbestos fibers show a sequence of events as they progress from normalcy to malignancy.

The stages of development of human cancers from epithelial cells in lung or ovarian malignancies called “carcinomas” are illustrated in **Figure 5**. The process begins by uncontrolled cell proliferation (hyperplasia) and proceeds to metaplasia, defined as a loss of normal cell function. These changes can be reversible, but as cells become progressively more abnormal (defined as dysplastic), they acquire further traits (increased survival, decreased resistance to programmed cell death and ability to grow under adverse conditions) that allow them to become malignant, i.e., a carcinoma-in-situ or tumor. Many carcinomas eventually invade normal tissues and metastasize to other organs. It is important to note that the reversible changes of cell proliferation and metaplasia by asbestos fibers can be documented in *in vitro* models, but whether these result in malignant tumors can only be assessed in animal studies.

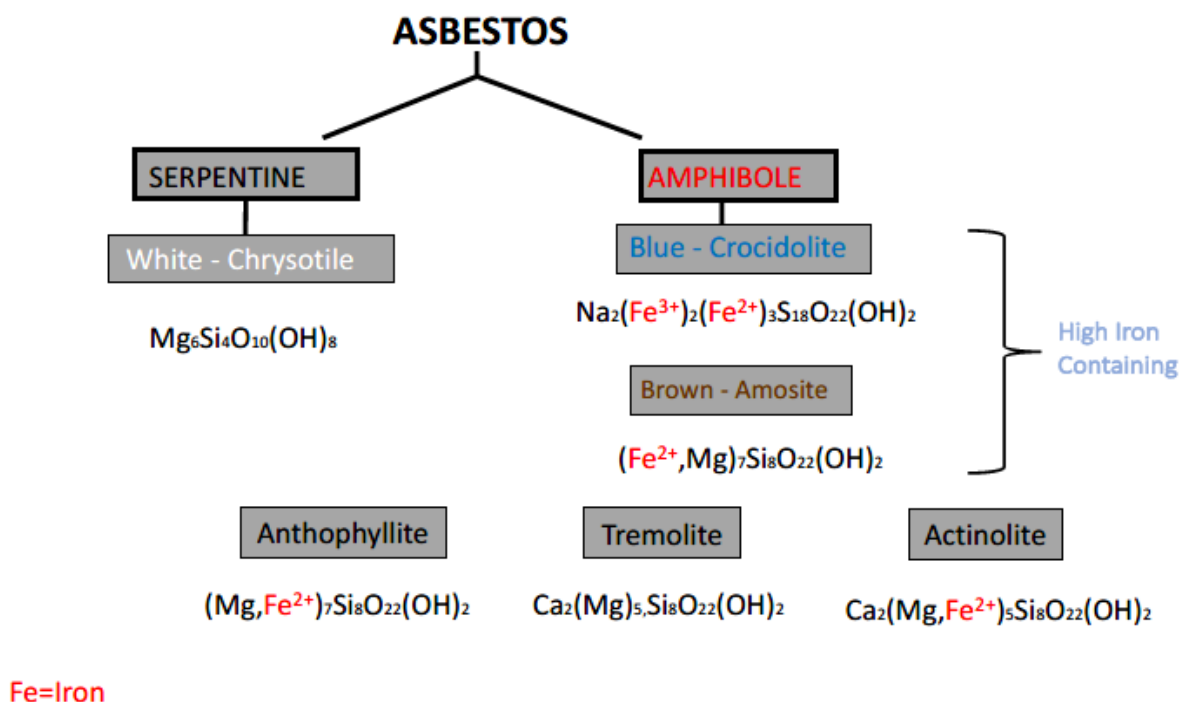
Figure 5. Sequence of events leading to the development of human tumors i.e. carcinomas.



IX. What Is Asbestos?

“Asbestos” is a commercial term that refers to two groups of minerals that crystallize in a certain formation or habit called “asbestiform” (**Figure 6**). “Asbestiform implies relatively small fiber thickness and large fiber length, flexibility, easy separability and a parallel arrangement of the fibers” (Guthrie and Mossman, 1993). There are five asbestos types (crocidolite, amosite, anthophyllite, tremolite and actinolite) in the amphibole group of asbestos and one type (chrysotile) in the serpentine group. These differ in their chemical composition (as indicated on Figure 6) as well as their mineral crystallization structure and other features.

Figure 6. Classification and composition of different asbestos types.



A. Epidemiologic studies showing different cancer risks of asbestos fibers in worker populations

Since asbestos fibers have been mined and used in industries worldwide for more than a century, it has become apparent that workers exposed to different types of asbestos have different risks of lung cancers and mesotheliomas. A striking confounder in analysis of lung cancer data is the fact that almost all asbestos workers historically have been smokers, which is an overriding factor in causation of lung tumors, but studies on mesothelioma, a tumor not influenced by smoking, have been informative in ranking risks of mesotheliomas by various types of asbestos. The increased risks of mesothelioma in crocidolite and amosite asbestos-exposed workers have been documented in many epidemiologic studies and are much higher than risks associated with exposures to chrysotile asbestos (reviewed in Craighead and Mossman, 1979; Mossman and Gee, 1989; Mossman et al., 1990; IARC, 1989; Health Effects Institute, 1991; Hodgson and Darnton, 2000). For example, the robust database on mesotheliomas in epidemiologic studies has recently been updated by Garabrant and Pastula (2018), who found that the relative potency of chrysotile:amosite:crocidolite was 1:83:376-fold. Data on relative risks of asbestos types in workers have resulted in the conclusion that “[a]lthough all forms of asbestos can cause mesothelioma, there is considerable evidence that the potency for the induction of mesothelioma varies by fibre type, and in particular that chrysotile asbestos is less potent than amphibole forms of asbestos” (IARC, 2012, p. 238).

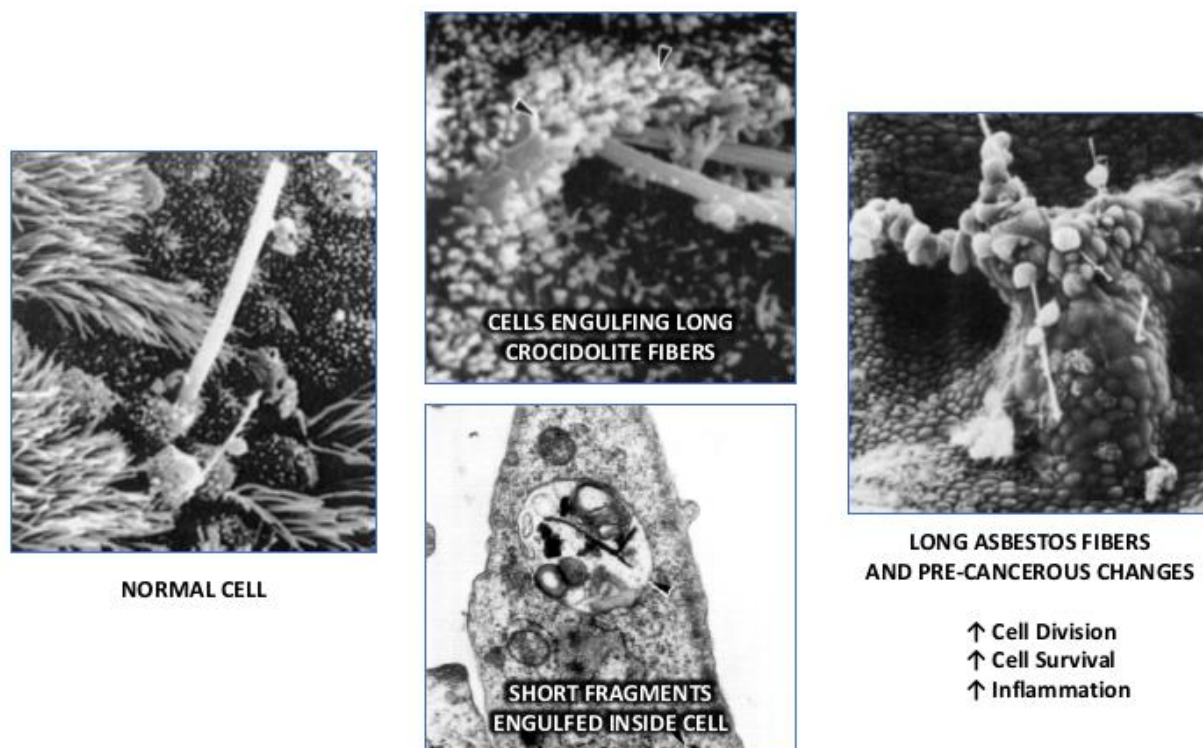
B. Importance of size, shape, chemistry and other characteristics of asbestos fibers in the cancer process – human tissues, animal studies and *in vitro* models

Fiber dimensions. Many properties of minerals are important in their toxicity and carcinogenicity. For example, more than a dozen different mineralogical features have been considered in developing a general model for predicting the cancer risks of mineral fibers (Gualtieri, Mossman and Roggli, 2017). Of these many properties, dimensions have been studied most extensively. Since the pleural injection studies of Stanton et al. (1981) who calculated in rodents that fibers > 8 microns in length and <.25 microns in diameter were most carcinogenic, it has been recognized that long, thin fibers are associated with chronic inflammation, lung cancers and mesotheliomas in rodents and humans (reviewed in Barlow et al., 2018; Roggli, 2015; Lippmann, 2014). For example, length-dependent retention of fibers, inflammation and injury has been demonstrated in animals exposed to a number of fiber types (Moalli et al., 1987; Donaldson et al., 1989; Donaldson et al., 2010; Murphy et al., 2011; Murphy et al., 2012; Schinwald et al., 2012; Murphy et al., 2013). Carcinogenicity studies using long vs. short fiber preparations in rodents also show that long fibers preferentially cause mesotheliomas and lung cancers (Pott, 1978; Davis et al., 1978; Spurny et al., 1979; Stanton et al., 1981; Davis et al., 1986; Berman et al., 1995; Chernova et al., 2017).

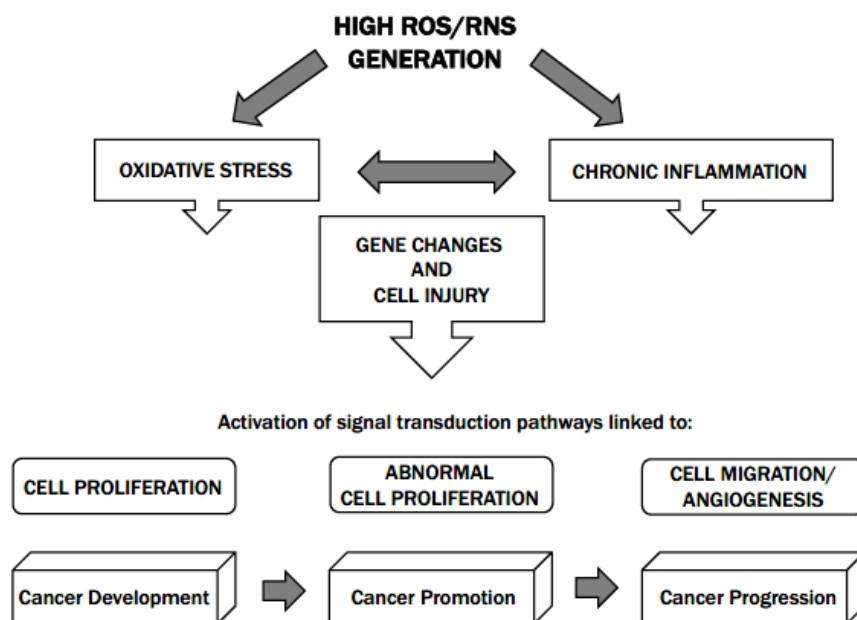
In the studies above, the cut-off value length of long fibers associated with tumor development was > 5 microns, as fibers of these dimensions have been measured in most studies by microscopy conducive to regulatory definitions. However, it has been emphasized recently that fibers 10 microns or greater in length are more representative of carcinogenic potency in humans based on analysis of human tissues (Roggli, 2015; Roggli and Green, 2019). It also has been stressed that human macrophages are > 16 microns in diameter and cannot engulf and remove larger fibers effectively (reviewed in Oberdorster and Graham, 2018).

Our studies have shown that lung epithelial and mesothelial cell responses to long and short asbestos fibers are different. As shown in the left panel of **Figure 7** using electron microscopy, normal cells come in contact with both long and short fibers. However, cells cannot completely engulf (phagocytose) long asbestos fibers (upper middle panel), whereas short fragments are incorporated into intracellular membrane-bound digestive structures for removal. We have shown that industrial talcs (Woodworth et al., 1982; Shukla et al., 2009) and a number of other non-disease-causing minerals, including cleavage fragments, are taken up by lung epithelial and mesothelial cells in a similar manner without causing toxic effects. The right panel of Figure 7 shows that long asbestos fibers remain on the surface of exposed cells for months to stimulate inflammation, increased cell division and altered cell appearance (i.e., metaplasia) in organ (mixed cell) cultures of the lung.

Figure 7. Different mechanisms of lung and mesothelial cell response to long (>5 microns) or short (<5 microns) fibers.



In other studies, we have documented that, in contrast to short fibers, long fibers (> 10 microns) cause significantly more oxidant release from macrophages (Hansen and Mossman, 1987; Mossman et al., 1989). Long fibers also stimulate membrane receptors and proteins linked to cancer development (Marsh and Mossman, 1988; Pache et al., 1998) as well as preneoplastic changes (Mossman et al., 1977; Woodworth et al., 1983 a,b,c). Others have shown that long fibers preferentially interact with chromosomes and cytoplasmic proteins affecting cell division (Cole et al., 1991; Ault et al., 1995; Jensen and Watson, 1999). **Figure 8** (adapted from Benedetti et al., 2015) shows links between oxidant generation and the development of cancers by crocidolite or amosite asbestos as demonstrated in our laboratory over the past 30-40 years. These show that high dose-dependent production of oxidants must occur over time to induce oxidative stress and alterations in gene/protein expression that activate cell signaling pathways leading to tumor development (reviewed in Shukla et al., 2009; Mossman, 2011; Mossman, 2013).

Figure 8. Mechanisms of high oxidant generation and cancer development by asbestos fibers.

Fiber shape. Unlike amphibole asbestos fibers, which crystallize in a straight, rodlike formation, chrysotile asbestos fibers form in tangled or helical bundles that impede their penetration into the finer airways and the deep lung. For these reasons, chrysotile fibers, in contrast to amosite or crocidolite asbestos, have diminished accumulation and persistence in lungs after inhalation (Wagner et al., 1976). It also has been shown that the dissolution or breakdown of chrysotile asbestos occurs due to the leaching of magnesium from fibers and separation of fiber bundles into smaller fibrils (reviewed in Mossman et al., 2011). This dissolution is also important in establishing why chrysotile asbestos is less durable in lungs and less apt to cause mesotheliomas in humans.

Fiber chemistry, flexibility, crystal structure and durability. In addition to the role of fiber dimensions and shape, other properties have been linked to mesothelioma development by amosite or crocidolite asbestos (reviewed in Mossman et al., 2011; Mossman et al., 2013; Shukla et al., 2003; Mossman, 2018). These include: 1) their high iron content, which drives production of oxidant species causing oxidation of DNA and stimulation of cell signaling pathways to malignancy; 2) surface availability of iron (Fe) in a form or surface charge that drives redox reactions. In this regard, Fe^{+3} on the surface of crocidolite asbestos drives chemical reactions producing toxic oxidants. Conversely, forms of iron such as ferritin, which comprises ferruginous bodies in the lung, do not drive these reactions and may be protective when minerals such as talc are coated by macrophages in the lung or pleura (Gualtieri, Mossman and Roggli, 2017); 3) flexibility or the ability of asbestos fibers to penetrate and move throughout the lung and pleura; 4) crystal structure and growth; and 5) ion exchange and dissolution. All of these properties affect fiber durability at sites of tumor development and the responses of cells to minerals (reviewed in Gualtieri, Mossman and Roggli, 2017).

C. Studies supporting the importance of dose, the existence of a threshold for asbestos-induced mesotheliomas, and other causes of mesothelioma

As discussed in **Section VI.** above, the importance of dose-related responses in the development of cancers is a fundamental tenet of toxicology. Epidemiologic studies on asbestos-related mesotheliomas have demonstrated that dose and duration of exposure in workplace environments are linked to risks of tumor development. Moreover, animal experiments in our laboratory (Quinlan et al., 1994; Quinlan et al., 1995; Shukla, Vacek and Mossman, 2004) and others (reviewed in Health Effects Institute, 1991; Mossman et al., 2011; Drummond et al., 2016) have shown that both hallmarks of disease development and tumors are dose-related. In rodent studies using both chrysotile and crocidolite asbestos, we measured inflammation, molecular changes (elevations in expression of genes linked to cancer development) and proliferation in lung epithelial and pleural mesothelial cells for periods as long as 40 days after initiation of exposures to two concentrations of asbestos. These studies showed no significant changes by asbestos types at concentrations far exceeding current occupational exposure limits set by regulatory agencies such as NIOSH.

In vitro experiments also show thresholds below which aberrations do not occur in response to various asbestos types (DiPaolo et al., 1983; Jaurand et al., 1986; Mikalsen et al., 1988; Oshimura et al., 1984; Palekar et al., 1988; Price-Jones et al., 1980). Thus, both *in vivo* and *in vitro* results indicate the existence of a threshold below which cell and tissue responses are not observed (reviewed in Mossman, 2018; Ilgren and Browne, 1991). These studies undermine the theory that a single or low dose of a carcinogen-causing mineral gives rise to cancer.

Many reports and reviews indicate other causes of mesotheliomas, including radiation and other mineral fibers such as erionite and fluoro-edenite (reviewed in Ilgren and Wagner, 1991; Kane, 1996; Gualtieri et al., 2018; Kraynie et al., 2016). Factors such as genetic predisposition (Testa et al., 2011; Ohar et al., 2016; De Rienzo et al., 2016), aging and spontaneous transformation of normal cells to genetically unstable or tumor cells (Fleury-Feith et al., 1989; Sherwood et al., 2008; Funaki et al., 1991) may also occur. These factors may explain the 15 to 20% of mesotheliomas occurring in individuals with no documented exposures to asbestos fibers (Kraynie et al., 2016; Attanoos et al., 2018).

X. What Is A Cleavage Fragment?

“Cleavage” is defined as “the property of an individual crystal to fracture or break along crystallographically defined planes determined by the structure of a mineral” (Guthrie and Mossman, 1993). Defined broadly, cleavage fragments can occur when amphiboles and other minerals are milled or crushed, but not after crushing of other materials, such as chrysotile asbestos or synthetic glass. It is important to realize that amphibole minerals “occur more commonly in a non-asbestiform habit [i.e., crystallized form], and may also be elongated [i.e., fibrous] without being asbestiform” (IARC, 2010, p. 277). Plaintiffs’ expert Mark Krekeler has opined that nonasbestiform minerals such as tremolite and anthophyllite that break into cleavage fragments during processing become “asbestiform particles with the same health risks as asbestos, due to the size, morphology and chemistry of the modified particles” (Krekeler Report,

pp. 3-4). This is not scientifically accurate. Cleavage fragments are not asbestiform and **not asbestos** by definition. The classification and nomenclature of respective asbestos types and their nonasbestos cleavage fragments are indicated in **Table 2**. Further, reliable studies demonstrate that exposure to cleavage fragments is not associated with the development of mesotheliomas or cancers (Addison and McConnell, 2008; Gamble et al., 2008; Chatfield, 2018; Garabrant and Pastula, 2018; Roggli and Green, 2018).

Table 2. Classification of asbestos fibers and non-asbestiform fragments

MINERAL FAMILY		ASBESTOS ASBESTIFORM	NON-ASBESTIFORM (including cleavage fragments)
Serpentine		Chrysotile	Antigorite/Lizardite
		Crocidolite	Riebeckite
		Amosite	Cummingtonite-Grunerite
Amphibole		Tremolite Asbestos	Tremolite
		Anthophyllite Asbestos	Anthophyllite
		Actinolite Asbestos	Actinolite

A. Different properties of cleavage fragments and amphibole asbestos fibers

Cleavage fragments differ from their asbestos counterparts in several important respects (**Table 3**). Most importantly, they differ in their dimensions because they cleave into blunt, thick fragments as opposed to amphibole asbestos, which breaks longitudinally into long, thin fibers. As discussed above, the diameter or width of fibers governs whether they are inhaled and how deep in the lung they can penetrate (reviewed in Mossman et al., 2011). For example, fibers > 3 microns in diameter do not generally get inhaled; fibers > 1.5 microns in diameter do not penetrate the deep lung; and fibers > 0.5 microns in diameter do not get out to the parietal pleura (Lentz et al., 2003). Measurements on cleavage fragment preparations show that fragments > 10 microns in length do not have widths < 0.5 microns, and thus will not get out to the pleura. Moreover, less than 0.05% of long cleavage fragments have widths < 0.25 microns (Wylie, 2016; email exchange with Dr. Wylie). Thus, amphibole cleavage fragments are unlikely to be inhaled or penetrate to the pleura, where mesothelial cells exist. The overall dimensions of cleavage fragments are also incompatible with the dimensions of amphibole asbestos fibers shown to be important in tumor development (Wylie, 2016; Roggli and Green, 2019).

Table 3. Properties of asbestos minerals important in cancer development

- **Dimensions (Long, Thin)**
- **Geometry (Rod-like)**
- **Crystal Structure and Growth**
- **Flexibility/Tensile Strength**
- **Chemical Composition**
- **Surface Area/Chemistry/Charge**
- **Durability***

*** All these properties are interlinked to persistence of fibers at sites of cancer development.**

Important differences in dose-responses to asbestos and cleavage fragments exist because unlike asbestos fibers, nonasbestos fragments do not break in a parallel fashion to create more long and thin fibers. There are also differences in flexibility between asbestos and nonasbestos fragments due to differences in their crystalline structure and growth. These factors may influence how cells respond to these materials. Lastly, crocidolite asbestos and its respective cleavage fragment, riebeckite, are different in that crocidolite asbestos generates oxidants via its iron content. Guthrie (1997) emphasizes the significant replacement of oxidant-generating iron by magnesium in riebeckite as compared to crocidolite asbestos. The dissolution of riebeckite by this process could also reflect a lack of durability of riebeckite fragments. Gunter et al. (2011) have also shown differences in iron chemistry of asbestiform and nonasbestiform amphibole minerals that explain why asbestiform amphiboles have more oxidant-generating capabilities. Lastly, surface defects and surface chemistry are different, and these factors are important in reactivity with cells (see below).

B. Animal studies demonstrate no cancers after exposures to cleavage fragments.

Chronic lifespan studies in rodents after administration of asbestos or nonasbestos fragments by a variety of routes have failed to demonstrate the development of mesotheliomas by cleavage fragments (**Table 4**). Most relevant to this discussion is a recent EPA study in which a number of naturally occurring asbestos types and an asbestos-like amphibole mineral from Libby, Montana were injected directly into the trachea of rats at two concentrations (Cyphert et al., 2015; Cyphert et al., 2016). Tumors occurred after exposures to the Libby amphibole, described as a transitional

asbestiform fiber, at high concentrations of minerals (i.e., millions of fibers) but not at 10-fold lower concentrations. In contrast, an iron-containing nonasbestos fragment, i.e., ferroactinolite, did not cause lung injury or tumors. This study indicates that it is not iron content *per se* that causes oxidant production, inflammation and injury. Moreover, results support the tenet of a threshold concentration of minerals below which tumors do not occur.

Table 4. Life time rodent studies show no mesotheliomas nor ovarian cancers after exposures to non-asbestos cleavage fragments and talcs

Study	Asbestos	Non-Asbestos Fragment*
Stanton and Wrench 1972,1981	All amphiboles +	Fibrous and platy talcs -
Wehner et al. 1972		Cosmetic talc -
Wagner et. al. 1975	Chrysotile +	Italian talcs
Stenback + Rowland, 1978		Fibrous talc -
Wagner et. al. 1980	Crocidolite +	Talc -
Wagner et al., 1982	Tremolite +	Tremolite -
Smith et. al., 1979		Fibrous talcs -
McConnell et al., 1983 (feeding studies)	Tremolite -	Tremolite -
Coffin et al., 1992	Amosite +	Grunerite -
Cyphert et al., 2016	Libby amphibole +	Ontario ferroactinolite -

C. *In vitro* studies demonstrate that cleavage fragments do not induce oxidant production and markers of inflammation and cancer development.

We have traditionally used cleavage fragment preparations of riebeckite in our *in vitro* models to determine whether mechanisms of action of crocidolite asbestos are unique or observed after exposures to particles in general. For these reasons, we have also used a number of nonasbestos fibers and particles to determine the properties of crocidolite and amosite fibers that are important in cell responses. Erionite and Libby amphibole fibers have been used as positive controls, i.e., minerals that induce cancer, and a number of particles not associated with cancer development, such as glass beads, titanium dioxide and polystyrene beads have been used as negative controls. In all studies, we and teams of geologists characterized the shape, dimensions and other characteristics of minerals and their toxicity to cells.

Experiments using crocidolite and nonasbestos riebeckite comparatively are listed in chronological order in **Table 5**. These studies generally focused on whether crocidolite, as compared to riebeckite, caused changes in oxidant generation, oxidative damage to cells, and signatures of early cancer development, including increased cell division and loss of normal function, i.e., metaplasia. In summary, studies on lung epithelial cells and mesothelial cells showed responses that were specific to crocidolite asbestos fibers and not observed with riebeckite fragments.

Table 5. Studies showing the lack of oxidative stress, inflammation and hallmarks of cancer development by non-asbestos fragments including talcs (Mossman laboratory in peer-reviewed literature)

Study	Asbestos Fibers	Non-Asbestos Fragments
Woodworth et al., <i>Cancer Res.</i> , 1983, Cell Division, Metaplasia	Crocidolite +	Riebeckite
Hansen and Mossman, <i>Cancer Res.</i> , 1987, Oxidant release	Crocidolite +	Riebeckite
Marsh and Mossman, <i>Cancer Res.</i> , 1988, Tumor promoting protein	Crocidolite +	Riebeckite
Heintz et al., <i>PNAS USA</i> , 1993, c-fos, c-jun, AP-1	Crocidolite +	Riebeckite
Janssen et al., <i>Am. J. Resp. Crit. Care Med.</i> , 1994, Antioxidant enzymes	Crocidolite +	Riebeckite
Janssen et al., <i>Am. J. Resp. Cell Mol. Biol.</i> , 1994, Early response genes	Crocidolite +	Riebeckite
Zanella et al., <i>Cancer Res.</i> , 1996, ERK1/2 Proteins	Crocidolite +	Riebeckite
Chen et al., <i>Carcinogenesis</i> , 1996, Oxidative DNA damage	Crocidolite +	Riebeckite
Janssen et al., <i>Am. J. Path.</i> , 1997, Cell survival protein	Crocidolite +	Riebeckite
Goldberg et al., <i>Am. J. Resp. Cell Mol. Biol.</i> , 1997, Programmed cell death	Crocidolite +	Riebeckite
Wylie et al., <i>Toxic. Appl. Pharm.</i> , 1997, Cell survival	Crocidolite +	NYS Talc* (11%, 37%, 59% fibers)
Zanella et al., <i>Am. J. Physiol.</i> , 1999, Cell receptor interference	Crocidolite +	Riebeckite
Shukla et al., <i>Am. J. Resp. Cell Molec. Biol.</i> , 2009, Increased gene expression	Crocidolite +	Talc
Hillegass et al., <i>J. Toxic. Environ. Health</i> , 2010, Differential gene expression	Crocidolite +	Talc
Taylor et al., <i>Langmuér</i> , 2013, Receptor stimulation	Crocidolite +	Riebeckite

XI. What Is Talc?

A. Different properties of talcs and asbestos fibers

Talc can be considered a cleavage fragment in the broadest use of this term because it is milled and crushed during and after mining. However, it should be emphasized that talc is distinct in form and chemical composition from amphibole cleavage fragments or chrysotile asbestos (Guthrie and Mossman, 1993). In this regard, its molecular formula contains magnesium and silica, but its crystalline structure is dissimilar. Unlike amphibole asbestos, which can persist in the body for the decades required for human tumor development, the estimated retention time for a talc particle in the body is approximately eight years (IARC, 2010, p. 281). Talc is insoluble (thus not to be confused with a chemical) and “has very little chemical reactivity” (IARC, 2012, p. 230). It has no positive charge, a factor linked to toxicity of chrysotile asbestos in many cell types (Craighead et al., 1980; Woodworth et al., 1982). In contrast to asbestos fibers, the shape of talc particles is plate-like and rarely fibrous. Fibrous talcs occur in some ores, such as those occurring in the Gouverneur mining districts of New York, that have not been exploited commercially for production of cosmetic or pharmaceutical talcs (IARC, 2010, p. 281; Wylie et al., 1997). In any event, as set forth below, there is no scientifically reliable evidence that fibrous talc is carcinogenic or that exposure to fibrous talc poses a health risk similar to that which is associated with asbestos fibers. Fibrous talcs not containing asbestos fibers have **not** been classified as human carcinogens (IARC, 2010, p. 412) and are structurally and chemically different from asbestos or asbestiform fibers.

Commercial talcs can be described as industrial (referring to mining samples or products containing minerals other than talc), cosmetic talcs that are more pure (> 98% talc) and pharmaceutical talcs (> 99% pure) used for medical procedures such as pleurodesis (IARC, 2012, p. 230; Zazenski et al., 1995). In the United States, the presence of asbestos in talc has been documented in a mining deposit in Death Valley, CA that has never been used for processing of cosmetic or pharmaceutical talcs (Van Gosen et al., 2004). Talc in the body does not have the same inflammatory and carcinogenic effects as amphibole asbestos fibers because of its different properties and purity.

B. Numerous studies in animals and humans exposed to high levels of industrial, cosmetic and pharmaceutical talcs do not demonstrate the development of mesotheliomas.

Table 4 above summarizes the results of life-time rodent studies designed to test whether administration of industrial or cosmetic talcs via a number of routes is cancer-causing. These and other studies summarized in IARC (2010) have evaluated the carcinogenicity of various talcs at high concentrations after inhalation or injections. Regardless of the route of exposure, studies using platy or fibrous talcs have failed to demonstrate tumor development. The results of animal studies have also been supported by epidemiologic studies in talc miners and millers that show no increased risk of mesothelioma (Rubino et al., 1976; Rubino et al., 1979; Coggiola et al., 2003; Addison and McConnell, 2008; Gamble and Gibbs, 2008; Anderson et al., 2017; Boffetta, 2018; Garabrant and Pastula, 2018; Pira et al., 2018).

Long-term follow-up of individuals after injection of pharmaceutical talcs into the pleural cavity also shows no inflammatory disease or tumors. Injection of talc particles into the pleural cavity has been used in treatment of human pleurodesis (collapse of the lungs) and to combat malignant effusions. This causes a transient inflammation and release of inflammatory cytokines that seal the damaged pleura. Multiple follow-up studies show that no mesotheliomas or ovarian cancers develop subsequently in persons undergoing these procedures (Clive et al., 2016; Kolschman, 2005; Hunt et al., 2007).

C. *In vitro* studies demonstrate that talc does not cause markers of inflammation and tumor development.

Studies by others have shown that talcs from various mining sites do not induce DNA damage or signatures of genotoxicity associated with initiation and development of mesotheliomas (Endo-Capron et al., 1993). Our experiments subsequently examined whether talc particles played a role in increased cell survival and proliferation of rodent lung epithelial and mesothelial cells (Wylie et al., 1997). We also measured injury to cells as indicated by decreased cell survival.

In these experiments, we added reference samples of crocidolite or chrysotile asbestos or 3 samples of New York fibrous industrial talcs. The total percentages of fibers were 11, 37 and 59 in talc preparations, and the mineral composition, chemistry, crystal structure and size of minerals were documented by geologists at Yale University and the University of Maryland. Samples of fibrous talcs also contained cleavage fragments of nonasbestiform tremolite and anthophyllite.

In brief, talcs and asbestos at multiple concentrations were added to cells for seven days, and the size of colonies of cells developing over this time period (an indication of cell survival) were measured. Rat mesothelial cells did not exhibit increased cell survival in response to either asbestos or talc samples, which was attributed to shortcomings of this assay when evaluating growth of individual cells in culture. However, exposures to both asbestos types caused increased survival of lung epithelial cells, whereas talc fibers did not, even when doses of fibers were controlled for approximately equal amounts of fibers > 5 microns in length, equal surface areas and other dose parameters. Thus, the proliferative responses we observed with asbestos could not be explained by differences in fiber dimensions or surface areas. These results indicate an important role of mineralogical composition and type, as opposed to dimensions alone, in induction of precancerous changes. Our results correlated with data on tumor development after injection of asbestos, New York talcs and other talc samples into animals (Smith et al., 1979; Stanton et al., 1981). Despite doses of talc fibers > 8 microns in length and < 0.25 microns in widths large enough to predict a tumor probability of > 50%, no excesses in tumor development were observed (Stanton et al., 1981). These studies also indicate that cleavage fragments of nonasbestiform tremolite and anthophyllite are not carcinogenic.

In subsequent research, we have examined the gene expression changes by crocidolite asbestos in comparison to a well-characterized platy industrial talc, glass beads and titanium dioxide (both non-cancer-causing particles, i.e., negative controls) in human mesothelial and ovarian epithelial cells (Shukla et al., 2009; Hillegass et al., 2010). After examining a range of concentrations of all

materials to determine toxicity, we used a low and high concentration of asbestos at eight hours to determine whether dose-responses in gene expression occurred in comparison to equal surface area concentrations of talc, glass beads and titanium dioxide particles. Cell death precluded the analysis of gene expression by high concentrations of asbestos at 24 hours; thus, talc at comparable high concentrations was not examined at this time point.

Results are presented in **Table 6**. In mesothelial cells, gene expression analyses in comparison to untreated control cells (no particle added) showed that changes in gene expression were dose-related and increased over time at low concentrations of asbestos. In contrast, talc produced less striking increases in gene expression that decreased over time. Unlike asbestos, talc did not down-regulate any genes. Ovarian epithelial cells were more resistant to toxicity and gene changes by asbestos, and no significant changes in gene expression were observed with talc. Glass beads and titanium dioxide did not induce significant gene changes in either cell type. Lastly, we performed experiments to determine the function of a specific gene (ATF3) that was significantly upregulated by talc at eight hours and asbestos at both time points to determine its functional role in inflammation. By blocking the expression of this gene in freshly isolated pleural mesothelial cells, we prevented the production of several proteins linked to asbestos-induced inflammation and cancers. Thus, ATF3 was characterized as a gene/protein that is anti-inflammatory and inhibits early markers of cancer development by asbestos.

A follow-up of this study showed that gene expression by talc was significantly different both qualitatively and quantitatively from asbestos (Hillegass et al., 2010). Another sophisticated method was used to compare dose and time-related patterns of talc-induced gene expression in relationship to asbestos (positive control) and glass beads/titanium dioxide (negative controls). These methods reconfirmed that gene expression by talc was equivalent to gene expression by non-cancer-causing control particles and untreated cells (no particle exposures) in human mesothelial cells and ovarian epithelial cells. In our experiments, gene expression was compared to respective protein expression and release in cells and did not correlate precisely. Thus, our results emphasize, as do many studies in the literature, that it is imperative to measure whether changes in genes (SNPs, etc.) correlate with levels, release and activity of proteins in mechanistic *in vitro* studies.

Table 6. Talc does not cause altered gene expression in human mesothelial or ovarian epithelial cells

<u>Groups</u>	<u>Mesothelial Cells</u>		<u>Ovarian Epithelial Cells</u>	
	24 hrs	8 hrs	8 hrs	24 hrs
1. Asbestos				
Low*	29	205	0	0
High	236	– Cell Death	2	17
2. Talc				
Low	1	0	–	–
High	30	–	0	0
3. Fine TiO ₂				
Low	0	0	–	–
4. Glass Beads				
High	0	0	0	0

* = Low concentration = 1µg/cm²; High concentration = 5 µg/cm².

– = Not examined

N.S. = Not significant statistically

In summary, my research data, review of the peer-reviewed scientific literature and relevant panel conclusions do not support the premise that either platy or fibrous talc causes mesotheliomas, lung cancers (in the absence of smoking) or ovarian cancers in animals or humans.

XII. Scientific Evidence Does Not Support The Hypotheses And Opinions Of Dr. Saed.

Qualifications: Ghassan Saed, Ph.D., has been an Associate Professor at Wayne State University for approximately 20 years. Dr. Saed testified that he has not applied to be a full professor because his institution “requires current NIH NCI only funding, which is very hard to get” (Saed Dep. Vol. I 279:11-17), but this explanation glosses over other, more fundamental weaknesses in Dr. Saed’s resume, most notably a lack of independent research funding and sporadic publications in low-impact journals. He states, “My laboratory investigates the role of oxidative stress in the pathogenesis of ovarian cancer” (Saed Report, p. 2). This research is limited to a few publications on identification of early markers of disease, and the roles of oxidative stress in chemoresistance exhibited by epithelial ovarian cancer cells (EOC). An Update/Review of the literature summarizes roles of oxidative stress at various stages of ovarian cancer development, but does not address talc (Saed, Diamond and Fletcher, 2017). Sources of funding are not disclosed on his “Update” article, which largely serves as the basis of his opinions on talc. It is

unclear whether this review, listed at least twice on his CV and multiple times in his report, was peer-reviewed. The funding sources of his past and current research on the development of ovarian cancers are unclear, and he is not listed as principal investigator on federal grants supporting his research. His CV lists several grants as pending or active that in fact should be expired according to their dates, and many others that have not been funded (Saed CV, pp. 21-26). In his January 23, 2019 deposition, Dr. Saed clarified that his time spent on talc research and the resulting article on the “molecular basis” of ovarian cancer were funded by plaintiffs’ counsel.

Dr. Saed’s sole membership historically on editorial boards for journals is limited to “Editor-in-Chief, Gynecology and Obstetrics Research-Open Journal- 2015-Present.” This journal is not indexed in PubMed (the largest research database in medical literature). Nor does it report an impact factor. This is highly unusual.

As outlined below, Dr. Saed’s opinions are not supported by his publications or others in the fields of toxicology and ovarian cancer development. His review of the literature is questionable, as many of his statements are unreferenced, referenced incorrectly, or listed, but not discussed in the text. Likewise, results and conclusions from peer-reviewed studies are often misconstrued or omitted if contrary to his opinions.

Ovarian Cancers: In his report, Dr. Saed states that the “pathophysiology of EOC is not fully understood but has been strongly associated with inflammation and the resultant oxidative stress” (Saed Report, p. 4 (citation omitted)). The reference cited is a general review article entitled “Oxidative stress, inflammation and cancer: How are they linked?” (Reuter et al., 2010). There is no mention of ovarian cancer in the text of this article. A citation by Chan et al. (2008) in Table 2 of Reuter et al. (2010) describes a signaling pathway mediated by oxidative stress that “enhances tumorigenicity and chemoresistance of ovarian cancer cells,” but these effects occur after cells have become malignant and are irrelevant to the **causation** of ovarian tumors. It should be acknowledged that Reuter and colleagues discuss the mechanisms “by which **continued** oxidative stress can lead to **chronic** inflammation, which in turn could mediate most chronic diseases including cancer, diabetes, and cardiovascular, neurological and pulmonary diseases” (Reuter et al., 2010, Abstract), and never mention talc as an agent inducing oxidants or cancers. In fact, inflammation has not been linked to the development of ovarian cancer, which explains why Dr. Saed is not able to cite any publication supporting that statement.

Sections on Oxidative Stress and Ovarian Cancer Cells Manifest a Persistent Pro-oxidant State in Dr. Saed’s report describe the importance of the balance between oxidative stress and antioxidant repair mechanisms. The statement on page 5, “[r]ecent evidence demonstrates that oxidative stress is a critical factor in the **initiation** and development of several cancers, including ovarian cancer” (Saed Report, p. 5 (emphasis added)), is not supported by the references cited (Saed et al., 2011; Senthil et al., 2004) that, to the contrary, refer to oxidative stress generated by anticancer agents in malignant ovarian cancers. Saed et al. (2011) and others (e.g., Senthil et al., 2004) have examined markers of oxidative stress in the circulation of ovarian cancer patients but this is a generalized response seen in many cancer patients *after* the development of tumors.

Dr. Saed then goes on to describe studies in which he has examined markers for early detection of ovarian cancer and genetic point mutations (SNPs) in antioxidant enzymes that may govern chemoresistance of EOCs to the chemicals cisplatin and taxotere. He cites his one paper (Fletcher et al., 2016) more than a dozen times throughout the text as showing that “[t]here is now an association of specific SNPs in key oxidant and anti-oxidant enzymes that impact increased **risk** of ovarian cancer” (Saed Report, p. 8). This statement is not supported by his research that examines SNPs induced by chemotherapeutic drugs with no relationship to ovarian cancer risks. Dr. Saed’s misinterpretation of his SNP findings and its lack of relationship to the development of ovarian cancers and his recent talc data are confirmed in his deposition (Saed Dep. Vol. I 201:17-209:4, 211:6-218:24).

In an attempt to link oxidative stress to the process of cancer development, Dr. Saed states, “[t]he oxidative damage to 8-Oxo2- deoxyguanosine, a major product of DNA oxidation, induces genetic alterations in oncogenes and tumor suppressor genes that have been involved in tumor initiation and progression” (Saed Report, pp. 9-10), again referencing Fletcher et al. (2016). In fact, Dr. Saed did not study oxidative damage to this DNA adduct in his cited study.

Talcum powder and increased risk of ovarian cancer (Saed Report, p. 10): This section is filled with inaccuracies in the text and misinterpretation of studies in the peer-reviewed scientific literature by my research group and others. His misstated references are detailed below.

- The statement, “In its natural form, some talc contains asbestos” (Saed Report, p. 10) is unreferenced and fails to acknowledge that the deposits from which Johnson’s Baby Powder and Shower to Shower have been sourced over time are not associated with asbestos contamination (Boundy, et al., 1979; Pira, et al., 2017). And ultimately, Dr. Saed testified at his deposition that the presence or absence of asbestos in cosmetic talcum powder products is irrelevant to his opinions (Saed Dep. Vol. I 264:2-5).
- His statement that “the carcinogenic effects of asbestos have been extensively studied and documented in the medical literature” references two papers. The first is one by our group (Haegens et al., 2005), in which we did **not** study carcinogenic effects of asbestos. In fact, we studied the development of pulmonary fibrosis, a nonmalignant disease, in mice with the capability to generate oxidants and mice without this capacity in short-term inhalation studies. The other reference he cites, Muscat and Huncharek (2008), also does **not** describe carcinogenic effects of asbestos. This paper is a review concluding that “[m]echanistic, pathology and animal model studies have not found evidence of a carcinogenic effect. In summary, these data collectively do **not** indicate that cosmetic talc causes cancer” (Muscat and Huncharek, 2008). It is unclear why Dr. Saed cites these irrelevant publications.
- Dr. Saed attempts to equate talc with asbestos fibers in his statement that “it has been proposed that ground talc, as a foreign body, initiates a similar inflammatory response and it has been proposed that ground talc, as a foreign body, might initiate an inflammatory response” (Saed Report, p. 10), again citing the Muscat and Huncharek

(2008) article and also a paper by Ness and Cottreau (1999). In contrast, as just noted, the review by Muscat and Huncharek (2008) concluded that perineal use of cosmetic talc does **not** cause cancer. The review by Ness and Cottreau (1999), entitled “Possible role of ovarian epithelial inflammation in ovarian cancer,” proposes the novel hypothesis that a common mechanism underlying ovarian cancer is inflammation via oxidative stress and cytokines, which may be mutagenic. A subsequent letter by Balkwill (2000) questions this simplistic comment, stating that “it is possible that inflammatory cytokines are important in the evolution of many different malignancies and not just epithelial ovarian cancer.” In essence, Dr. Saed has stolen these ideas as a basis for his emerging scientific research without referencing either of these citations in his recently accepted paper.

- Dr. Saed states that “[t]here has been concern about a possible link between talcum powder usage in the genital [area] and ovarian cancer, as well as lung cancer in workers exposed to talc in an occupational setting” (Saed Report, p. 10), citing a paper by Karageogi et al. (2010). This group studied the possible relationship between use of talcum powder and **endometrial** cancer risk, found no statistical association, and concluded that future and larger studies were needed. No references are provided to support Dr. Saed’s statement regarding “lung cancers in workers exposed to talc in an occupational setting” (Saed Report, p. 10). In fact, many cohort studies show the **lack** of mesothelioma development in talc miners and millers (Rubino et al., 1976; Rubino et al., 1979; Coggiola et al., 2003; Gamble and Gibbs, 2008; Addison and McConnell, 2008; Anderson et al., 2017; Boffetta et al., 2018; Garabrant and Pastula, 2018; Pira et al., 2018). These many peer-reviewed papers are not referenced in Dr. Saed’s report.
- Dr. Saed states that “[s]tudies that exposed lab animals (rats, mice and hamsters) to asbestos-free talcum powder in various ways have had mixed results, with some showing tumor formation and other finding only inflammation” (Saed Report, p. 10-11), citing only two references. But again, these references do not support his statement. The paper by Graham and Graham (1967) injected a huge amount of **tremolite asbestos (not talc)** into the peritoneum of animals and did not find asbestos fibers in the ovaries after this route of administration. The other reference is an epidemiologic study by Langseth and Kjaerhaim (2004), in which they did not study inflammation by pathology or other measures. This study looked at ovarian cancers in Norwegian pulp and paper workers exposed to asbestos, talc or both dusts. The authors state that “[t]he results do not confirm an association between exposure to asbestos, talc, and total dust and ovarian cancer” (Langseth and Kjaerhaim, 2004, Abstract).
- Dr. Saed also misstates the conclusions of the IARC panels in 2010 and 2012 and obviously did not review the many life-time rodent studies showing neither mesothelioma nor ovarian cancer development by exposure to talcs. Moreover, fibrous, non-asbestiform talcs were not classified as human carcinogens by IARC (2010) as Dr. Saed claims.

- On page 12 of his report, Dr. Saed states, “The ability of talc particles to migrate through the genital tract to the distal fallopian tube and ovaries is well documented,” citing two references. This statement is **not** supported by the first reference, his Update review (Saed et al., 2017), nor the study referenced (Kunz et al., 1997). These researchers used labeled protein spheres of sperm size that were placed at the entrance of the cervical canal. This artificial means of applying a soluble protein in no way resembles perineal application of talc, and the authors state that “a large proportion of the macro spheres remains at the site of application.” Dr. Saed conceded this error at his deposition. (Saed Dep. Vol. I 322:6-323:20.)
- No support is provided for Dr. Saed’s conclusion that migration and accumulation of talc occurs in the ovary. In fact, although he references the IARC (2010) monograph above, he fails to state the conclusions: “[o]n balance, the [w]orking [g]roup believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak...[s]tudies in animals (rodents, langmorphs and non-human primates) showed no evidence of retrograde transport of talc to the ovaries” (IARC, 2010, p. 411).
- On page 12, Dr. Saed also states, “It has been suggested that the associations between perineal talc dusting and ovarian cancer might be explained by the induction of ANTI-MUC1 antibodies.”⁵⁷ This reference is to a paper by Cramer et al. (2005) suggesting that talc might affect systemic immunity. Dr. Saed does not reference the subsequent Letters to the Editor by other scientists, including one stating that “the conclusion about genital talc exposure increasing ovarian cancer risk via diminished antibody levels is not supported by their own data...this speculative assumption was ruled out years ago by electron microscopy studies showing no relationship between genital dusting and ovarian talc particle concentrations” (Muscat and Huncharek, 2005).
- On page 12, there is also a sentence referencing our peer-reviewed study contrasting gene alterations by crocidolite asbestos and talc in human mesothelial cells and ovarian epithelial cells (see Table 6 above). Dr. Saed does not mention our results showing **no** changes in gene expression in human ovarian cells after exposure to talc, limits his text to our results in mesothelial cells, and states that “the authors found that nonfibrous talc at low concentrations [caused] an increase in the expression of Activating Transcription Factor 3 (ATF3) ...” He does not acknowledge that ATF3 was characterized as an **inhibitor** of inflammation in our studies, and that unlike asbestos, no changes in gene expression were observed at 24 hours in mesothelial or ovarian epithelial cells after exposures to talc. Most importantly, he fails to state that talc changes on cell viability and gene expression were significantly less than those found with asbestos and comparable to negative control dusts not associated with disease causation, i.e., fine titanium dioxide and glass beads.
- Dr. Saed does not reference our follow-up study, in which gene expression was compared in both mesothelial and ovarian epithelial cells after exposure to asbestos, talc and control

particles (Hillegass et al., 2010). These studies confirmed that talc-induced gene alterations were quantitatively and qualitatively different from asbestos and comparable to the negative control particles, titanium dioxide and glass beads.

- On pages 13-20, Dr. Saed describes recent experiments from his laboratory on ovarian cancer cell lines, macrophages, and ovarian epithelial cells exposed to two cosmetic talcum powders for **24 hours**. For reasons that are unclear, he added four concentrations of talcs diluted and suspended in DMSO (dimethylsulfoxide), a toxic solvent chemical used to solubilize water-insoluble chemicals. It is likely that DMSO coated the surfaces of the talc particles, and changed talc's normal reactivity with cells. He also does not use a positive toxic agent, such as asbestos, or a negative control agent (an inert particle such as glass beads), prerequisites for interpretation of his results. In brief, he measures RNA expression and protein levels of antioxidant/oxidant-related enzymes and a protein marker that can be elevated with the onset of ovarian cancer (CA-125) in cell medium. The data from this study, including results and statistical significance, are not presented in Research Findings (Saed Report, p. 16) although it is stated that "[r]ecent studies from our laboratory have shown **conclusively** that talcum powder alter[s] key redox and inflammatory markers, enhance[s] cell proliferation in EOC cells, which are hallmark of ovarian cancer" (*id.*). Again, Dr. Saed's research update summary (Saed et al., 2017) is referenced repeatedly, but this paper does not present any original data on talc exposures. Statements such as "[c]ollectively, these findings demonstrate that talc treatment induced gene point mutations that happen to correspond to SNPs in locations with functional effects" (Saed Report, p. 19) are not supported by his scientific data as presented here. In attempting to attribute findings of SNPs to treatment with talc, Dr. Saed is trying to make a case for mutations by talc in the causation of ovarian cancer. However, it has been demonstrated historically in many cell types that asbestos fibers are not mutagenic using a number of assays (reviewed in Mossman, 2018). Thus, findings as presented below in his manuscript (Fletcher et al., in press) with talc are unusual and incredible due to the short time frames of talc exposures, i.e., 24 to 72 hours. Moreover, the statement, "In summary, this research clearly demonstrates that talcum powder induces inflammation and alters the redox balance favoring a pro-oxidant state in normal and EOC cells" makes no sense as Dr. Saed did not examine inflammation, an orchestrated response of many cell types, in his short *in vitro* experiments. He also did not measure oxidant release from cells or oxidative stress directly in his cell cultures, important prerequisites for conclusions on the oxidant state of cells.
- Dr. Saed's in-press manuscript (Fletcher et al., in press) was apparently shared with other plaintiffs' experts, including Dr. Zelikoff (Zelikoff Dep. 55:3-24). The research and preparation of this manuscript by Dr. Saed was funded by plaintiffs' attorneys. It serves as the sole basis supporting the theory that talcum powder causes oxidative stress, inflammation and ovarian cancer. The paper, in which Dr. Saed claims to describe a "molecular basis" for how talcum powder causes transformation of normal ovarian cells to cancer cells, is severely flawed, and the data it presents are unconvincing. He has not

demonstrated a link between talc and ovarian cancer development. Moreover, he failed to state in his initial submission of the manuscript to *Gynecologic Oncology*, as required by the Conflicts of Interest forms for that journal, that his study is funded by plaintiffs' attorneys and that he has been paid substantially as a consultant for them. Instead, he stated on page 13 of his submission, "The authors have no conflicts of interest to declare." My conclusions on the lack of merit of his findings are supported by the original reviewers who rejected the paper. In reviews of his paper received on 9/19/2018, Reviewer #1 states, "In this reviewer's opinion the cell line studies alone and the increase in CA-125 while intriguing are not sufficiently convincing." Reviewer #1 also states, "The significance of SNP alterations should be further clarified." And most importantly, "The first bulleted highlight, 'Oxidative stress is a key mechanism to the initiation and progression of ovarian cancer' is not supported by this investigation and should be omitted." Reviewer #2 states "their data do not show, despite the authors' claim, any evidence that these cells are transformed. Specifically, no experiments documenting changes in cell survival, proliferation or resistance to apoptosis have been performed. Consequently, neither tumor initiation nor progression is documented in this study as opposed to the statement in Highlight #1 and elsewhere. While changes in redox potential play an important role in tumor biology in general, the present data are insufficient to back up the claim that talcum is central to the development of ovarian cancers. ... The fact that SNPs were changed following such short exposure to talcum is surprising and makes one wonder what the biological effect of such changes may be." It is important to note that the data submitted in this paper were after exposures of cells to talc samples for **48 hours (which Dr. Saed remarkably now claims was a typographical error)** (Saed Dep. Vol. I 185:6-186:7; Saed Dep. Vol. II 487:15-25). This time point is stated several times in the submitted paper, including the Abstract, Methodology, Results and Figure Legends. In conclusion, the editorial decision on this paper was rejection with the editorial comment, "Please note that a revised version of the current manuscript should not be submitted for another review to *Gynecologic Oncology*." Instead of truthfully reporting the substance of the reviewers' comments at his January 23, 2019 deposition, Dr. Saed stated, "[y]eah, they like it, they love my work" (Saed Dep. Vol. I 49:3).

- To address the short time frame of exposure questioned above as "surprising," Dr. Saed recently resubmitted his paper to the lower-impact journal *Reproductive Sciences*. In this paper, he supposedly presents data from exposures to talc over a 72-hour period. It should be noted that the same data in Figures 1-4 from the *Gynecologic Oncology* submission at 48 hours are now presented using identical Figure Legends 1-4, with the exception that 48 hours has been changed to 72 hours in each Figure legend and on the ordinate of all graphs. In Figure 1, panels A, C and D are the same as in the previous manuscript, and panel B has been changed. In Figure 2, panels B, C and D are the same as the previous submission, but Panel A is different. In Figure 3, panels C and D are the same, and Panels A and B are different, and Figure 4 is identical, but 48 hours has now been changed to 72 hours in the Figure legend. In summary, Dr. Saed now presents most of his 48-hour data as 72-hour data. This misrepresentation of data is a blatant example of scientific

misconduct. The manuscript was submitted to Dr. Lawrence Layman, an Associate Editor of the journal. Dr. Layman is in the same department and University as Dr. Michael Diamond, a co-author of Dr. Saed's Update/Review article (2017), the principal investigator of Dr. Saed's past research on ovarian cancers, and his former business partner in Dr. Saed's consultant enterprise, DS Biotech (Saed Dep. Vol. I 284:11-285:18). Dr. Saed also reveals in this deposition that he was first retained and paid for this work in 2017 (*id.* 38:13-16). In addition to misrepresenting the time points of his study and the many concerns expressed by reviewers after his submission to *Gynecologic Oncology*, I note other discrepancies in time points of talc exposures between what is reported in his expert report, abstracts (see below) and his two manuscript submissions. It is impossible to assess his research data, which are often not presented as original values. Other graphs present data as a percentage of controls, and statistical significance values are not included on figures, as would be required in most peer-reviewed journals. Instead, Dr. Saed inserts the sentence, "All changes in response to talc treatment were significant ($p < 0.05$) in all cells as compared to controls" on all figures (Fletcher et al., in press, p. 15). He also states in every figure legend that "[e]xperiments were performed in triplicate," when in fact his testimony and notebooks show that this is false (*id.*). There are many flaws in the methodology used. For example, the MTT assay, which measures cell metabolism, is misinterpreted as an assay measuring cell proliferation (Hillegass et al., 2009).

- Contrary to instructions for submission of papers to *Reproductive Sciences*, Dr. Saed does not relate his research funding source or disclose his conflicts of interests in this manuscript. Since his studies were funded by plaintiffs' attorneys, these are serious breaches of scientific conduct. Dr. Layman has expedited publication of this paper with Comments to the Author from only one reviewer, who replies in three brief sentences, including the notation that the manuscript is "wordy." Dr. Saed apparently resubmitted the paper that was received with the Comment: "Well done" and acceptance of the paper by Dr. Layman on 1/14/2019. This superficial and expedited review of a submitted paper is very unusual.
- I was also asked to review Dr. Saed's laboratory notebook (SAED000001-000097) that he presented for the studies reported in his manuscript. This is not a normal laboratory notebook, which should present daily and sequential entries and information on cell counts, observations, raw data and details on individual experiments. Instead, the notebook lists abbreviated standard methodology (either hand-written or pasted from other documents, cell sources with no details on their growth characteristics or responses to talc by microscopy) and has been "cut and pasted" to include or exclude sample ID numbers from spreadsheets, and final figures from his manuscript before all data were analyzed statistically at the end of the notebook (SAED000093-000097). Data entry was often not in normal sequence and there were often large gaps in time between entries, suggesting that the notebook was put together "after the facts." It was impossible to examine much of the raw data, but Dr. Saed stated during his deposition that only one

sample per individual cell type was examined in each assay and that numbers that appeared to differ from groups were thrown out of the data set. This scientific misconduct was attributed to his technician and a statistician who determined outliers according to his deposition testimony. Especially alarming were the lack of details and statements such as “[c]ells doubled in one day” (SAED000002 (dated Jan. 29, 2018)). Normal ovarian epithelial cells would never double in one day. The method of talc dilution and exposure also makes no sense in that concentrations from 2.5 to 50 microliters (SAED000004 (dated Feb. 2, 2018)) were apparently added to cells in medium. These minute volumes could in no way cover the surfaces of cells in a Petri dish. This suggests that cells were not exposed to talcs.

- In conclusion, the statements in Dr. Saed’s “[s]ummary of opinions” (Saed Report, pp. 20-21) are **not supported** by his research results, peer-reviewed studies in the scientific literature or conclusions of panels of scientists. He does not exhibit knowledge of relevant scientific literature, list peer-reviewed papers on mechanisms of cancer development by asbestos, or include references showing the lack of cancer development by talc. He has not published any credible peer-reviewed papers on research from his laboratory in peer-reviewed journals in the fields of toxicology and cancer research, and his data, as recently submitted to *Reproductive Sciences*, are flawed and unrealistic from many standpoints. His manipulation of research data and time points and failure to declare conflicts of interest or bias in the funding of and publication of his research results are serious issues of scientific misconduct that should be brought to the attention of his co-authors and the Editor of *Reproductive Sciences* before his article is published. He alludes to his research data, stating that “the molecular effects resulting from Johnson’s Baby Powder exposure exhibits a clear dose-response pattern,” but does not support this statement and others with his data or references in the peer-reviewed scientific literature. His final opinion that “Johnson’s Baby Powder exposure worsens the prognosis for patients with ovarian cancer” (Saed Report, p. 21) is highly speculative, unfounded and unreferenced.

XIII. Scientific Evidence Does Not Support The Hypothesis And Opinions Of Dr. Zelikoff.

Background and Qualifications: Dr. Zelikoff obtained her Ph.D. in Experimental Pathology and Immunology in 1982 and is a tenured faculty member in Toxicology at the NYU Institute of Environmental Health Sciences.

Methodology: As a general matter, Dr. Zelikoff purports to have followed a rigorous methodology in preparing her report, but many aspects of her approach were not scientific. She relies heavily on expert reports by plaintiffs’ other experts, as well as depositions and internal documents supplied by plaintiffs’ counsel, none of which are legitimate scientific literature and all of which have biased her opinions and conclusions. Indeed, Dr. Zelikoff conceded that she did not attempt to ensure that she was provided with documents that tell the entire story, especially with respect to asbestos testing results (Zelikoff Dep. 275:13-276:20). Although she claims to have performed searches of the scientific literature, many high-impact, peer-reviewed

scientific papers on talc and ovarian/lung cancers are not listed in her Materials and Data Considered or referenced in the text of her report. Others are listed but not described accurately. A review of Materials and Data Considered shows that she also relies heavily upon abstracts, opinion papers and book chapters that are not peer-reviewed. Finally, several of her statements were cut and pasted from the reports of other experts or the Internet without citation, further calling into question the reliability of her statements (*see* Zelikoff Dep. 75:10-124:15).

Dr. Zelikoff claims that her opinions only concern biological plausibility, not causation (Zelikoff Dep. 72:23-73:16, 130:22-131:12). She emphasizes that, for her opinions, “[b]iological plausibility does not mean proof of mechanism” (Zelikoff Report, p. 2). Dr. Zelikoff has indeed not supplied proof of a mechanism through which talc use causes ovarian cancer. The issues discussed in this section demonstrate the serious methodological deficiencies in her attempt to posit that a mechanism is even plausible. In fact, each section of her report contains numerous errors in her text, references and interpretation of results that undermine her credibility and conclusions.

Talc, Asbestos and Heavy Metals (Zelikoff Report, pp. 3-12). Dr. Zelikoff’s discussion of fibrous talc, asbestos and other alleged talc contaminants demonstrates a misunderstanding of fundamental concepts of minerology and inaccurately presents the data regarding whether cosmetic talc products are contaminated and/or unsafe due to the alleged contamination.

- In her discussion of Fibrous Talc (Zelikoff Report, p. 4), Dr. Zelikoff, like Dr. Saed, misstates the conclusions of the 2010 and 2012 IARC panels in her statement that “[i]n its fibrous form, talc has been classified as a Group I, known carcinogen.” In fact, only talc containing asbestos or asbestiform fibers was considered to be a Group 1 carcinogen (IARC, 2012); fibrous, non-asbestiform-containing talcs were not (IARC, 2010). Dr. Zelikoff repeatedly confuses fibrous talc with talc containing asbestos. Fibrous talcs do not induce tumors in animals (Smith et al., 1979; Stanton et al., 1981), nor pre-malignant changes in rodent epithelial and mesothelial cells (Wylie et al., 1997), as explained in peer-reviewed literature that was not cited by Dr. Zelikoff. She also fails to reference studies by Wagner (Wagner et al., 1975; Wagner et al., 1980) and others, which show that talc does not produce mesotheliomas or lung malignancies after administration to animals by a variety of routes.
- Dr. Zelikoff’s discussions of Asbestos and Asbestos in Talc (Zelikoff Report, pp. 5-8) contain numerous mistakes. Dr. Zelikoff does not claim to be an expert in asbestos or minerology (Zelikoff Report, pp. 1-2; Zelikoff Dep. 162:20-164:24). This is evident throughout many sections of her report where Dr. Zelikoff equates nonasbestos amphiboles and serpentine fibers with asbestos and fails to differentiate between asbestiform and non-asbestiform fibers. Moreover, the studies Dr. Zelikoff cites in attempting to show that “the presence of asbestos in cosmetic talc has been reported in the literature” (Zelikoff Report, p. 6 (citing Rohl et al., 1976, Paoletti et al., 1984, and Cralley et al., 1968)) have been questioned by other scientists and panels. For example, Dr. Zelikoff fails to cite a response by Krause and Ashton (1978) questioning

misidentification of asbestos in the Rohl et al. (1976) study. The IARC 2010 panel reached similar conclusions regarding these three papers, noting, among other things, that no data were provided to support the statement that “some [fibers] may have been anthophyllite, tremolite, pyrophyllite or chrysotile” in the Cralley et al. (1968) study, and that “no information was provided on the concentration of minerals, including tremolite and quartz” in the Paoletti et al. (1984) study (IARC, 2010, pp. 303-305). Finally, in arguing that a single fiber of asbestos or talc would supply a plausible biological mechanism (a theory that has been consistently rejected in the scientific community), Dr. Zelikoff misquotes a deposition by Robert Glenn, whom she describes as “[t]he former Director of National Institute for Occupational Safety and Health (NIOSH).” Mr. Glenn was never the Director of NIOSH. Moreover, Dr. Zelikoff conceded that she did not fully read Mr. Glenn’s deposition and failed to cite his statements that talc is not genotoxic or mutagenic (Zelikoff Dep. 548:20-549:8).

- In her section on Heavy Metals (Zelikoff Report, pp. 8-12), Dr. Zelikoff describes three heavy metals: nickel, chromium and cobalt, which have been classified as carcinogens or probably carcinogens by IARC panels, but again misrepresents the scientific data. Specifically, she references the Cralley et al. (1968) paper (which, as noted above, was discounted by the IARC 2010 panel) in support of the statement that “[s]tudies here suggest that women who used talcum powder in the 1960s could have been exposed to considerable amounts of toxic heavy metals depending on the type of talc used and frequency of use” (Zelikoff Report, p. 10). However, in these and other studies cited, heavy metals were found in miniscule amounts (parts per million) or found at “levels to be within safe limits” in talcum powders purchased off the shelf (*id.*, p. 11). Dr. Zelikoff also concurs with the expert report of another plaintiffs’ witness, Dr. Michael Crowley, who “concludes that fragrance chemicals may contribute to the inflammatory response, toxicity and potential carcinogenicity of Johnson & Johnson’s talcum powder products” (Zelikoff Report, p. 12). This statement is flawed from many standpoints, most notably that the trace chemicals Dr. Crowley lists have not been shown to be carcinogens in humans or animals, even at high amounts. In any event, Dr. Zelikoff conceded that none of the studies she cites in support of her theories regarding heavy metals and fragrances have to do with ovarian cancer or inflammation in the ovaries (Zelikoff Dep. 281:1-282:8; 291:14-24; 313:21-314:14). Nor did she compare whether the amounts of metals at issue in the studies she cites are similar to the doses women would be exposed to from metals allegedly present in cosmetic talc products (*id.* 295:12-17).

Exposure – Talc Particle Access to the Body (Zelikoff Report, pp. 12-17). Dr. Zelikoff’s opinions regarding talc exposure routes – including that “[a]nimal and human studies demonstrate that talcum powder products can migrate from the perineal region to the ovaries” (*id.*, p. 14) and that “[t]here is substantial evidence in the scientific and medical literature that support a conclusion that talc powder particles can reach the ovaries through inhalation” (*id.*, p. 17) – are also not supported by the scientific data.

On pages 12 to 17, Dr. Zelikoff speculates that talc can migrate upwards through the female reproductive tract, i.e., retrograde migration. In support, she cites a series of studies performed decades ago where boluses of talc were applied intravaginally or within the uterus, **not** externally to the perineum. She acknowledged, however, that there are no studies showing that talc applied externally (i.e., to the perineum) migrates to the ovaries (Zelikoff Dep. 339:21-340:14). Dr. Zelikoff attempts to bolster her opinion with limited studies in humans including a case report demonstrating the presence of talc particles in the pelvic lymph nodes of a woman with ovarian cancer (Cramer, 2007). But a single case report is not strong scientific evidence, and there could be other explanations for this finding. In any event, the same body of literature Dr. Zelikoff relies on was examined by the IARC 2010 panel, which concluded: “[o]n balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak...[s]tudies in animals (rodents, langmorphs and non-human primates) showed no evident of retrograde transport of talc to the ovaries” (IARC, 2010, p. 411). As IARC further observed, the positive findings in some studies in humans, such as after surgical procedures, “may be confounded by the various levels of dysfunction in clearance from the female reproductive tract due to underlying pathologies” (*id.*).

- Pages 14-15 of Dr. Zelikoff’s report summarize the results of inhalation studies showing that fine and ultrafine particles of a variety of types are inhaled and have been detected at distal sites in the body. After inhalation by animals, very small particles can enter the blood stream or lymphatic channels to accumulate in regional lymph nodes, as has been shown in the general population (Dodson et al., 2000). However, as Dr. Zelikoff conceded, there are **no** peer-reviewed studies demonstrating that inhaled talc causes inflammation in the ovaries (Zelikoff Dep. 302:2-303:10).

Mechanisms of Cancer (Zelikoff Report, pp. 17-21). Dr. Zelikoff’s general discussion of cancer mechanisms also contains a number of inaccuracies and incorrect assumptions, demonstrating that her methodology was not rigorous or sound.

- Dr. Zelikoff’s discussion overlooks that there are multiple histological subtypes of ovarian cancer, all of which are likely not caused by the same mechanism. Dr. Zelikoff conceded that she did not analyze the biological plausibility of ovarian cancer by subtype of ovarian cancer, and offered no opinion as to whether the subtypes have the same etiology (Zelikoff Dep. 193:11-195:7).
- Dr. Zelikoff also omitted crucial data and incorrectly presented other data. On pages 17-19, Dr. Zelikoff provides an overview of the cancer process, emphasizing the importance of genetic mutations by genotoxic carcinogens. However, she fails to acknowledge a critical peer-reviewed paper showing that talc particles from three different mining sites in Europe, including Italian, Spanish and French talcs, were **not** genotoxic to mesothelial cells. In contrast, both chrysotile and crocidolite asbestos induced markers of DNA damage (Endo-Capron et al., 1996). Similarly, on page 19, Dr. Zelikoff concludes that “Reducing immunity to MUC1 could be one mechanism by which talc increases endometrial and/or ovarian cancer risk” (Zelikoff Report, p. 19 (citing Karageori et al.,

2010)). But Karageorgi et al. (2010) studied the possible relationship between use of talcum powder and **endometrial** (not ovarian) cancer risk, found no statistical association, and concluded that future and larger studies were needed.

- Dr. Zelikoff's description of the processes of acute and chronic inflammation on pages 19-21 fails to acknowledge that talc (unlike cigarette smoke and asbestos) is not associated with chronic inflammation or tumors in the lung, pleura or elsewhere. As summarized by the IARC 2010 panel, "[t]alc is cytotoxic to macrophages and may be able to induce fibrosis and chronic inflammation in animals [after large injections]. However, the macrophage response to talc appears to be weaker than for other fibrogenic dusts such as quartz" (IARC, 2010, p. 398). As summarized in **Section VI. D** above, chronic inflammation by asbestos, silica and cigarette smoke may lead to cancers, but this should not be confused with the nonmalignant disease pulmonary fibrosis. We have known for decades that chronic inflammation fosters growth and angiogenesis of malignant tumors of a variety of types. However, talc's theorized action as a chronic inflammatory agent producing excessive oxidants in the initiation or development of ovarian cancer is highly speculative and illogical when considering the many properties of talc particles that render it inert and dissimilar to asbestos, silica or cigarette smoke.
- Finally, several other statements by Dr. Zelikoff in her description of Ovarian Cancer and Inflammation (Zelikoff Report, pp. 20-21) are unsupported by her references. For example, she states that "[r]ecent clinical and prospective data suggest that C-reactive protein (CRP), a marker of global inflammation, is associated with increased ovarian cancer risk" (Zelikoff Report, p. 20 (citing Li, 2017; Poole, 2013; Jing, 2017)). Poole and colleagues measured three plasma markers of inflammation (CRP, IL-6 and TNFaR2) in prospectively collected samples from the Nurses' Health Study I and II and the Women's Health Study, all of which found no link between talc usage and risk of ovarian cancer (Gertig et al., 2000; Gates et al., 2010; Houghton et al., 2014). Indeed, Poole found no significant associations between IL-6 or TNFaR2 protein expression and ovarian cancers, observations refuting Dr. Zelikoff's hypotheses that these are important inflammatory mediators in the causation of talc-induced inflammation and cancer (Zelikoff Report, pp. 21-24). Moreover, Dr. Zelikoff makes numerous errors in citing a study by Wu et al. (2009) on page 21. First, she omits that a major purpose of the Wu study was to examine the effect of NSAIDs on incidence of ovarian cancer, and that it found that ovarian cancer incidence did not decrease with increasing frequency and years of NSAID use – which is highly inconsistent with the inflammation theory (Zelikoff Dep. 471:20-474:4). Second, she ignores that the paper by Wu and colleagues was a very small study in LA County involving approximately 600 patients diagnosed with ovarian cancer, and that the authors discuss the many limitations and inconsistencies in their studies and other patient studies in the literature.

Mechanisms of Inflammation (Zelikoff Report, pp. 21-27). This section is replete with instances in which Dr. Zelikoff contradicts fundamental elements of cellular biology, incorrectly characterizes the scientific data and speculates.

- Dr. Zelikoff's conclusions regarding inflammation do not take into account the fact that talcum powder is used as an **anti-inflammatory** agent in applications to the dermis of the genital area such as diapering. In fact, there are **no** human studies suggesting that talc causes inflammation in the female reproductive tract. Dr. Zelikoff's conclusion that a "talcum powder-induced [inflammatory] cascade provides significant biologic and toxicologic support for a conclusion that talcum powder products can cause ovarian cancer" (Zelikoff Report, p. 26) is unfounded and not supported by peer-reviewed scientific data.
- In the introduction to this section, Dr. Zelikoff incorrectly cites several studies. First, the review by Maccio and Madeddu (2012) (cited in Zelikoff Report, p. 21) addresses the importance of proinflammatory cytokines on "promoting ovarian tumorigenesis and cancer progression," as well as the risk of ovarian cancer to incessant ovulation, but does not discuss or mention talc as an inflammatory or cancer-causing agent. In addition, on page 22, Dr. Zelikoff cites an outdated review (Ness and Cottreau, 1999) entitled "Possible role of ovarian epithelial inflammation in ovarian cancer." Those authors' conclusions were subsequently questioned by Balkwill (2000), who stated that "inflammatory cytokines in the tumor microenvironment might not contribute to genetic damage initiating cancer, but could be a fuel that promotes the cancer process." This argues against a role of talc in initiating ovarian cancers, as it does not cause damage to DNA, genetic damage or chronic inflammation. A more recent review, Landen et al. (2008), which Dr. Zelikoff fails to cite, presents a model of ovarian cancer that incorporates the roles of tumor cell mutations and the host microenvironment in initiation and development of tumors. This model precludes a role of talc in initiation and progression of ovarian cancers, as talc does not cause genotoxic changes or mutations in cells (Muscat and Huncharek, 2008; Endo-Capron et al., 1993; EPA, 1992; IARC, 2010).

Dr. Zelikoff's sections on Cytokine Networks and Macrophages (Zelikoff Report, pp. 22-24) contain numerous errors. The talc uptake by macrophages that has been shown in studies is most likely related to normal defense mechanisms. Moreover, Dr. Zelikoff's comparisons between fine and nanoscale talc are unjustified, since nanoscale talc would be a miniscule fraction, if any occurred in cosmetic talc (Zazenski et al., 1995). And although it is well documented in the nanotoxicology field that nano-sized materials of a variety of types are more toxic to cells than fine, larger particles, it is highly speculative to link toxicity as manifested by cell injury and death (problematic in *in vitro* studies using massive concentrations of talc, as in Dr. Saed's experiment) to mechanisms of cancer induction. Simplistically, dead cells or injured cells that cannot divide cannot give rise to premalignant or malignant cells. Dr. Zelikoff's comparisons between plasma concentrations of cytokines in ovarian cancer patients (Poole et al., 2013; Trabert et al.,

2014) and levels in cells or animals exposed to talcs are unjustified.

- Dr. Zelikoff's discussion of Macrophages (Zelikoff Report, p. 22-23) also severely mischaracterizes our Shukla et al. (2009) study. Specifically, Dr. Zelikoff fails to mention that we examined gene expression in human ovarian epithelial cells, in addition to mesothelial cells. These and additional data were examined subsequently by Hillegass et al. (2010) to show that effects of talc were comparable to those shown with the negative control particles, fine titanium dioxide and glass beads. She also misinterprets our data on Activating Transcription Factor (ATF3), the only gene upregulated at an early time point at low concentrations of talc in mesothelial cells. Dr. Zelikoff states that ATF "modulates production of pro-inflammatory cytokines and growth factors in human lung cells" (Zelikoff Report, p. 23), but fails to mention that it is a **negative** regulator of these inflammatory proteins. We also stated that "our experiments suggest that human mesothelial cells adapt to or undergo repair after exposure to [talc]" (Shukla et al., 2009). Finally, Dr. Zelikoff's subsequent statement that talc "caused increased expression of transcription factors associated with the inflammatory process in a **time** and dose-dependent manner" (Zelikoff Report, p. 26 (emphasis added) (citing Shukla et al., 2009)) is incorrect.
- The discussion on Talc-Induced Inflammation and Oxidative Stress (Zelikoff Report, pp. 25-26) likewise contains a number of inaccuracies and citation errors. Basic principles of toxicology and the importance of dose-response relationships are ignored in Dr. Zelikoff's initial statement that "[e]ven a single dose of a carcinogen can produce effects that are adverse to cells and tissue at the site of exposure" (Zelikoff Report, p. 25). This statement also ignores the fundamental tenet that injury and repair occur at low or single applications of cancer-causing agents. It is highly problematic that Dr. Zelikoff completely failed to consider the dose threshold needed to trigger the inflammatory mechanism around which her opinions center. Dr. Zelikoff acknowledged that dose contributes to the toxicity and carcinogenicity of an agent (Zelikoff Dep. 262:6-15; 343:10-17), but could not identify the threshold dose of talc necessary to start the biologic process for ovarian cancer (*id.* 263:14-266:15). Her unsupported opinion that a single particle of talc could trigger inflammation leading to ovarian cancer (*id.* 370:8-372:11, 373:16-22, 439:14-441:18) ignores the importance of dose, as does her reliance on studies where animals or cells were exposed to artificially huge amounts of talc that are nothing like the exposures in perineal talc use.
- Among other citation issues in this section is Dr. Zelikoff's summary of the Buz'Zard and Lau (2007) study. She cites this publication to illustrate "a well-established methodology called a neoplastic cell transformation assay" (Zelikoff Report, p. 25). However, Dr. Zelikoff neglects to mention that the assay she describes measures lack of contact growth of cells in culture, whereas cells must be injected into animals to ascertain whether they are cancerous. In fact, the neoplastic transformation data presented in Figure 2 (Buz'Zard and Lau, 2007, p. 581) shows that 2 to 9% of the two supposedly

“normal” ovarian cell lines (controls not exposed to talc) in their experiments grew in soft agar suspension. Thus, these cells were already neoplastically transformed, since, as Dr. Zelikoff correctly observes, “non-neoplastically-transformed cells cannot grow in suspension” (Zelikoff Report, p. 25). Moreover, as demonstrated throughout the Buz’Zard study, the supposed talc effects were neither dose-related nor consistent in each cell type. More importantly, the authors did not use proper positive (asbestos) or negative (inert particle) controls in their experiments, as would be necessary to draw conclusions about talc effects.

- Dr. Zelikoff’s heavy reliance on the Buz’Zard study is problematic for additional reasons related to that paper’s own improper citation of studies. First, it cites to Van Dyke et al. (2003) (which Dr. Zelikoff includes in her list of materials considered but does not directly cite). But the Van Dyke study stated that links between these short term-*in vitro* assays, chronic inflammation and cancer induction by talc are not justified – undercutting the notion that the Buz’Zard study can support inflammation as a mechanism for talc causing ovarian cancer. Specifically, these authors stated in describing their *in vitro* model: “If macrophages are exposed to particles *in vivo*, a totally different scenario occurs... Certainly one would not observe chronic inflammation which by definition takes weeks to occur inside an animal” (Van Dyke et al., 2003, p. 119). Their study also showed that superoxide (oxidant) release by talc from macrophages is minimal when compared to surface active minerals such as bentonite. Second, the Buz’Zard study discusses a paper by Dr. Zelikoff’s former colleague at NYU, Dr. Kevin Driscoll. In citing the Driscoll study, the Buz’Zard authors state: “[i]n an *in vitro* study of rat cells, both macrophages and neutrophils were found to be mutagenic in response to alpha-quartz dust, talc and diesel soot; however, neutrophils appeared to have a greater mutagenic effect” (Buz’Zard and Lau, 2007, p. 585 (citing Driscoll et al., 1997)). This study is misquoted, as Dr. Driscoll examined alpha-quartz, carbon black and titanium dioxide and **not talc** in these studies.
- Dr. Zelikoff’s claim that a study by Keskin et al. (2009) supports “a plausible mechanism for talcum powder-induced ovarian cancer” (Zelikoff Report, p. 25) further shows that she was not careful in reviewing and drawing conclusions from the scientific data. In this chronic study, a bolus of talc was applied daily either intravaginally or to the perineal area of rats for three months. The authors concluded: “[t]alc has unfavorable effects on the female genital system. However, this effect is in the form of foreign body reaction and infections, **rather than being neoplastic**” (Keskin et al., 2009, p. 925, Abstract). They also stated: “Even asbestiform talc is not as carcinogenic as asbestos owing to its chemical and physical properties” (Keskin et al., 2009, p. 926).
- Dr. Zelikoff primarily relies on two non-peer-reviewed abstracts by Dr. Saed’s laboratory (Zelikoff Report, pp. 25-26 (citing Fletcher, 2018, and Harper and Saed, 2018)) to support her opinion that the cosmetic talc products at issue cause oxidative stress, inflammation and ovarian cancers. Notably, neither of these abstracts is discussed or

referenced in Dr. Saed's expert report. And neither discloses its sources of materials, funding of the research or conflicts of interest.

- It is a significant stretch for Dr. Zelikoff to contend that the sparse content of these abstracts supports her opinions. Specifically, the Fletcher and Saed (2018) abstract claims to have exposed four ovarian cancer cell lines (EOC) and normal ovarian cells to huge amounts of talc (**200** and **500** micrograms/per ml medium) for 24, 48 or 72 hours. They note increases in pro-oxidant and decreases in anti-oxidant gene expression at 24 hours, as might be predicted with any toxic particle exposure, but no statistical analysis is presented to substantiate the "marked" changes they describe or whether these changes increase or decrease with time. The lack of positive and negative control particles, viability assays, and direct measurements of oxidative stress in cells makes these data virtually uninterpretable. It should also be emphasized that these studies are only measuring the mRNA levels, and not proteins or enzyme activities necessary to draw conclusions. Similar concerns preclude interpretation of the findings of the Harper and Saed (2018) abstract. Here, they claim to examine gene point mutations in key oxidant enzymes after exposures to talc (**100** micrograms per ml medium) for 48 hours in both ovarian cancer cells and normal ovarian epithelial cells. They also examine enzyme activities. They list a statistical method in the Methods, but do not present statistical significance values in their table of results. This study's raw data, as well as verification of results by statistical analyses (not to mention its origin and source of funding) should be scrutinized before drawing any conclusions from it. Dr. Zelikoff could not possibly have done her analysis based on these abstracts alone.
- Finally, Dr. Zelikoff's narrative regarding Iron-Facilitated Inflammation attempts to make a case for iron in the generation of talc-induced oxidative stress and inflammation, citing studies by Ghio et al (Ghio et al., 1992; Ghio et al., 2012). Those studies measured disturbances of iron metabolism in mesothelial cells in response to 100 micrograms/ml talc, characterizing that dose as "massive" (Ghio, 2012, p. 80, Abstract). Dr. Zelikoff fails to mention subsequent studies by Ghio et al. (2016) that demonstrated that "exposure of cells to **all** particulate matter, including air pollution particles," causes a disruption in iron metabolism in various cell types (Ghio et al., 2016 (emphasis added)). Many materials causing these changes are not carcinogenic.

Summary of Opinions (Zelikoff Report, pp. 27-28). As explained above, Dr. Zelikoff's conclusions are **not** supported by peer-reviewed scientific papers in the literature or basic tenets of toxicology and carcinogenesis. Conclusion #1 is based solely on her examination of reports by plaintiffs' experts claiming that there are carcinogens such as asbestos, heavy metals and fragrance chemicals in cosmetic talc. Conclusion #2 – that talc reaches the ovaries to cause cancer – is also not supported by peer-reviewed scientific literature or panels of scientists. Conclusion #3, claiming that talc causes changes in cell signaling, gene alterations and/or mutations, is contrary to published studies from our and other laboratories. No support exists for the opinion that talc causes

“[n]eoplastic transformation and proliferation” (*id.*, p. 28) in ovarian or other cell types. Moreover, her linking of talc to “[i]nhibition of apoptosis” (*id.*, p. 27) is contrary to published studies showing that talc induces apoptosis, i.e., programmed cell death, in human malignant mesothelioma cells without affecting normal mesothelial cells of the pleura (Nasreen et al., 2000). The sheer number of instances in which the actual reported data do not support Dr. Zelikoff’s opinions is strong evidence that she did not reliably consider the scientific evidence she claims to rely on and that her opinions are unscientific and speculative.

XIV. Conclusions

- 1) Drs. Saed and Zelikoff both betray a fundamental misunderstanding of the makeup of talc versus asbestos and the peer-reviewed and published research on ovarian cancer.
- 2) None of their opinions is supported by peer-reviewed published scientific research.
- 3) Based on Dr. Saed’s plaintiff-funded research, plaintiffs’ experts propose that talc causes a “pro-oxidant” state in ovarian epithelial cells that then causes chronic inflammation and tumor development. As emphasized above, no conclusions can be drawn about the importance of oxidative stress at the massive concentrations of talc used in the Saed studies. In addition, talcs were added to cultures in a toxic solvent, and proper positive and negative control minerals were not employed. In fact, the responses reported are seen at high exposures to a variety of non-disease-causing agents.
- 4) Contrary to statements in the text, Dr. Saed’s *in vitro* cell cultures cannot measure inflammation, which is an orchestrated response of many cell types of the immune system to foreign matter. He did not measure oxidative stress, inflammation (which takes months or years to develop) or cell proliferation directly in his experiments.
- 5) Neither chronic inflammation nor tumors are observed in long-term, follow-up studies on patients after talc pleurodesis, providing further evidence that chronic inflammation by talc is not linked to cancer development.
- 6) Dr. Zelikoff does not understand the difference among various asbestos types or the differences between asbestos and cleavage fragments.
- 7) There is no scientifically plausible pathway of migration to the ovary or oviducts or fallopian tubes by cosmetic talc particles. Since the IARC 2010 panel’s conclusions stating that there were no scientific studies supporting the phenomenon of retrograde talc movement from the perineal region to the oviducts and ovary, no new studies have demonstrated the existence of a putative pathway or mechanism for the transport of talc in this manner.
- 8) Dr. Saed’s and Dr. Zelikoff’s inflammation theories ignore – and are rebutted by – the available scientific research about talc and about the development of ovarian cancer. Although chronic inflammation may play a role in development of some tumor types, it has not been shown to play a role in ovarian cancer. To the contrary, pelvic inflammatory

disease (PID) and chronic tubal injury or inflammation are not significant risk factors for ovarian cancer (Rasmussen et al., 2016; Malmberg et al., 2016; Zhou et al., 2017). Moreover, evidence regarding any association between aspirin use and anti-inflammatory drugs with reduced risk of ovarian cancer is inconclusive (Ni et al., 2012). In sum, the relevance of chronic inflammation to the establishment of ovarian tumors is far from established.

XV. Glossary Of Terms And Abbreviations:

Amosite: a type of asbestos in the amphibole group

Amphibole: a broad term for a group of chain silicate mineral with a double chain structure

Angiogenesis: development of blood vessels

Anthophyllite: a type of asbestos in the amphibole group

Apoptosis: programmed cell death

Asbestiform: a subset of fibrous minerals implying long fiber length and small fiber thickness

Asbestos: a commercial term applied to the asbestiform varieties of serpentine (chrysotile) and amphibole asbestos types

Asbestosis: a nonmalignant disease of the lung associated with asbestos exposures

Bolus: a large amount or growth

Carcinogen: a cancer-causing agent

Carcinoma: epithelial cell tumor

Co-carcinogen: an agent interacting with a known cancer-causing agent to facilitate the development of cancers

Chrysotile: an asbestiform serpentine variety of asbestos

Cleavage: the property of a crystal to fracture or break along certain planes

Crocidolite: a type of asbestos in the amphibole group

Cytokines: proteins that are produced from cells to favor inflammation or disease

DNA: deoxyribonucleic acid capable of directing its own synthesis

Dysplasia: abnormal tissue development

EOC: epithelial ovarian cancer cells

Epidemiology: the study of human populations

Epigenetic: occurring by processes not affecting the DNA structure

Extracellular: outside the cell

Fibrosis: the formation of fibrous tissue, usually as a reparative or reactive process

Genotoxicity: property of an agent for altering the genome of cells resulting in cell death or altered function and division of cells

IARC: International Agency for Research on Cancer

Inflammation: a fundamental pathologic process consisting of a dynamic complex in response to an injury or abnormal stimulation

Intracellular: within the cell

In vitro: maintenance of cells or tissues outside of the body

In vivo: in the body

Macrophages: cells of the immune system with phagocytic functions

Mesothelioma: tumors arising from mesothelial cells

Metaplasia: altered cell function

Mutation: a heritable alteration in the DNA

Neoplasm: a new growth that is benign or malignant

Neutrophils: cells of the immune system that originate in the bone marrow or at other sites and are released into the circulation

NIH: National Institutes of Health

Nucleus: an organelle of the cell containing the genetic material

Pathology: the study of disease

Pathogenesis: the processes

Phagocytosis: process of elimination by cell uptake

Pleura: membranes enveloping the lungs and lining the walls of the chest cavity

Pleurodesis: a therapeutic process where talc is injected to seal the pleura

RNS: reactive nitrogen species

ROS: reactive oxygen species

Talc: a mineral species that is a 2:1 layer silicate

Talcosis: a fibrotic, noncancerous disease of the lung associated with heavy talc exposures in the workplace

Threshold: the point at which a stimulus is just strong enough to be perceived or produce a response

Toxicity: adverse effects by noxious or poisonous substances

Toxicology: the study of toxic substances

Tremolite: a type of asbestos in the amphibole group

EXHIBIT A

Dr. Brooke Mossman
Prior Deposition and Trial Testimony

Date	Case	Type
—	Case Sealed by Court (Minnesota)	Deposition
July 15, 2014	<i>Fishbain v. Colgate-Palmolive Co., et al.</i> , Case No. MID-L-5633-13AS (Superior Ct. of NJ)	Deposition
Mar. 12, 2015	<i>Winkel v. Calaveras Asbestos, Ltd, et al.</i> , Case No. BC549253 <i>Whitted-Justice v. Colgate-Palmolive Co., et al.</i> , Case No. 5:13-CV-00622-D (E.D.N.C.) (CA Super. Ct.)	Deposition
Aug. 21, 2015	<i>Goldsmith, et al. v. ACandS, Inc., et al.</i> , Consolidated Case No. 24X11000783 (Baltimore Circuit Ct.)	Deposition
Sept. 2, 2015	<i>Goodrich Corp. v. AG Securitas, et al.</i> , Case No. 2008-08-5847 Ohio (Court of Common Pleas)	Deposition
Jan. 22, 2016	<i>Owens v. American Truetzschler, Inc., et al.</i> , Case No. 2014-CP-30-772 (SC Court of Common Pleas)	Deposition
Apr. 6, 2016	<i>Alfaro v. American Talc Co. et al.</i> , Case No. BC583520 (CA Super. Ct.)	Deposition
June 15, 2016	<i>Nosse v. Arvinmeritor, Inc., et al.</i> , Case No. BC603354 (CA Super. Ct.)	Deposition
June 16-17, 2016	<i>Alfaro v. American Talc Co. et al.</i> , Case No. BC583520 (CA Super. Ct.)	Trial
June 22, 2016	<i>LaMonica v. Colgate-Palmolive, et al.</i> , Case No. BC604809 (CA Super. Ct.)	Deposition
July 15, 2016	<i>Nosse v. Arvinmeritor, Inc., et al.</i> , Case No. BC603354 (CA Super. Ct.)	Trial
July 18, 2016	<i>Polakow et al. v. Brenntag North America, Inc., et al</i> Case No: BC599542 (CA Super. Ct.)	Deposition
August 26, 2016	<i>Depoian and Depoian v American International Industries, Inc., et al</i> J.C.C.P. No. 4674 (CA Super. Ct.)	Deposition

Sept 16, 2016	<i>LaMonica v. Colgate-Palmolive, et al.</i> , Case No. BC604809 (CA. Super. Ct.)	Trial
Sept. 26, 2016	<i>B.Jackson v. Colgate-Palmolive</i> Case No. 1:15-CV-01066 (US District Court of Columbia)	Deposition
Sept. 30, 2016	<i>Depoian and Depoian v American International Industries, Inc.</i> J.C.C.P. No. 4674, (CA Super. Ct.)	Trial
Oct. 2, 2016	<i>A Blount v. Colgate Palmolive, et al.</i> Case # BC617806 (CA Super. Ct.)	Deposition
Oct. 11, 2016	<i>All Asbestos Litigation Filed by Gori, Julian & Assoc PC</i> Case No: 14-L-999002 (3 rd Circuit Madison, IL)	Deposition
Nov. 21-22, 2016	<i>A Blount v. Colgate Palmolive, et al.</i> Case # BC617806 (CA Super Ct.)	Trial
Nov. 29, 2016	<i>M Lyons, v. Metropolitan Life Insurance Co, et al.</i> , Case No. CGC16276495 (San Francisco Super Ct.)	Deposition
April 5, 2017	<i>S Foster v. Cyprus Amex Mineral Company, et al.</i> , Case No. RG15764371 (CA Superior Ct.)	Deposition
April 17, 2017	<i>D Greene v. ACandS, Inc., et.al.</i> Case No. 24X15000563 (Circuit Ct. Baltimore, MD) <i>E Link v. ACandS, Inc., et.al.</i> Case No. 24X15000557 (Circuit Ct. Baltimore, MD)	Deposition
May 12, 2017	<i>B Humphrey v. Akzo Nobel Paints, f/k/a Glidden Co., et al.</i> Case No. 16 L 45 (6 th Judicial Circuit Ct., Macon County, GA)	Deposition
July 10, 2017	<i>S Hanson v. Colgate-Palmolive Company, et al.</i> Case No: 2:16-cv-34 (US District Ct. GA, Brunswick Div.)	Deposition
July 14, 2017	<i>C Schoeniger v. Colgate-Palmolive Company, et al.</i> Docket No: MID-L-5869-1AS and <i>L Bartlow v. Colgate-Palmolive Company, et al.</i> Docket No: MID-L-5358-16AS, (Superior Court of NJ, Law Division – Middlesex County)	Deposition

August 11, 2017	<i>B Wittman, and J Wittman, v Brenntag North America, etc. et. al.</i> Case No: BC646439., (CA Super. Ct. for the County of Los Angeles)	Deposition
August 30, 2017	<i>T Herford and D Herford, Plaintiffs v. AT&T Corp., et al.</i> Case No: BC646315, (CA Super. Ct. for the County of Los Angeles)	Deposition
August 31 & September 14, 2017	<i>R Booker and C Booker, v. Cyprus Amex Mineral Company, et al.</i> Case No: RG15796166, (CA Super. Ct. for the County of Alameda)	Deposition
September 18, 2017	<i>S Jenkins v Avon Products, Inc., et al.</i> Case No: JCCP4674/ 37-2016-00025572, (CA Super. Ct, San Diego)	Deposition
September 19, 2017	<i>RA Stevenson and R Stevenson v MCIC et al.</i> Case No: 24-X-87048500 (Circuit Ct. for Baltimore City, MD)	Deposition
October 10, 2017	<i>D Chapp v Colgate Palmolive et al</i> Case No: 15-CV_____ Case Code: 30100 (Circuit Ct. for Milwaukee County, WI)	Deposition
October 13, 2017	<i>R Abeyta v A&A Building Material Co., Case No:</i> BC598586 (Superior Court of California, County of Los Angeles)	Deposition
December 19, 2017	<i>J Brooke v Honeywell International Inc., Case No: 16-2-21021-0 SEA</i> (Superior Court of Washington for King County)	Deposition
January 10, 2018	<i>J Ratcliff v BorgWarner Morse Tec LLC, et al., Case No:</i> 16-2-18128-7 SEA (Superior Court of Washington for King County)	Deposition
February 19, 2018	<i>J Minneci Estate v Johnson & Johnson, et al., Case No:</i> 2017-CA-000999-O (Circuit Court of the 9 th Judicial Circuit In and For Orange County, Florida)	Deposition
February 23, 2018	<i>R Berg v Alta Building Material Co., et al., Case No:</i> RG17849293 (Alameda County Superior Court, Oakland, CA)	Deposition

March 2018	<i>S Lanzo v Cyprus Amax Minerals Company, et al.</i> , Docket No. MID-L-7385-16AS, (Superior Court of New Jersey Law Division, Middlesex County)	Trial
March 30, 2018	<i>J Anderson v Imerys Talc America, Inc., et al.</i> , Case No. BC666153, (Superior Court of the State of California for the County of Los Angeles)	Deposition
March 30, 2018	<i>C Weirick v Imerys Talc America, Inc., etc.</i> , Case No. BC656425, (Superior Court of the State of California for the County of Los Angeles)	Deposition
April 10, 2018	<i>E Martinez v Honeywell International Inc., etc.</i> , Case No. 17-2-269000-0SEA, (Superior Court Washington for King County)	Deposition
April 10, 2018	<i>D Trepanier v Honeywell International Inc., etc.</i> , Case No. 17-2-25830-0SEA, (Superior Court Washington for King County)	Deposition
April 24, 2018	<i>N Cabibi v Avon Products Inc., et al.</i> , Case No. BC665257, (Superior Court of the State of California for County of Los Angeles)	Deposition
April 27, 2018	<i>I Brick v Brenntag North America, Inc., et al.</i> , Case No. BC674595, (Superior Court of the State of California for the County of Los Angeles)	Deposition
May 18, 2018	<i>I Delacruz v Brenntag North America, Inc., et al.</i> , Case No. BC658576, (Superior Court of the State of California for the County of Los Angeles)	Deposition
May 22, 2018	<i>B Boyd-Bostic v Sonoco Products Company, et al.</i> , C/A No. 17-CP-16-0400, (In the Court of Common Pleas, Fourth Judicial Circuit, State of South Carolina, County of Darlington)	Trial
June 18, 2018	<i>B Arend v Johnson & Johnson, et al.</i> , Docket No. MID-L-1370-17AS, (Superior Court of New Jersey Law Division, Middlesex County)	Deposition
July 9, 2018	<i>K von Salzen and J von Salzen v American International Industries Inc., et al.</i> , Docket No. BC680576, (Superior Court of the State of California for the County of Los Angeles)	Deposition

July 17, 2018	<i>J Alexander, et al.</i> v Honeywell International, Inc., et al., Case No. 868152, (The Court of Common Pleas, Cuyahoga County, Ohio)	Deposition
August 28, 2018	<i>D Waters, et al.</i> v AGCO Corporation, et al., Case No. 2017-CP-CP05462, (The Court of Common Pleas, County of Richland, State of South Carolina)	Deposition
September 10, 2018	<i>A Tucker</i> v Chanel Inc, et al., Case No. 17CV13605, (Circuit Court of the State of Oregon for the County of Multnomah)	Trial
September 11, 2018	<i>C Weirick</i> v Brenntag North America, Inc., et al., Case No. BC656425, (Superior Court of the State of California for the County of Los Angeles)	Trial
September 18, 2018	<i>C Allen</i> v Brenntag North America, Inc., et al., Case No. DR180132, (Superior Court of the State of California for the County of Humboldt)	Deposition
October 1, 2018	<i>C Hayes</i> v Colgate-Palmolive Company, et al., Case No. 16-CI-03503, (Jefferson Circuit Court, Division 10, State of Kentucky)	Deposition
October 22, 2018	<i>M Chapman</i> v BASF CATALYSTS LLC, Case No. MID-L-02911-17-AS; <i>R Rimondi</i> v BASF CATALYSTS LLC, Case No. MID-L-02912-17; <i>J Ruman</i> v BASF CATALYSTS LLC, Case No. MID-L-02919-17 (Superior Court of New Jersey Law Division, Middlesex County)	Deposition
October 23, 2018	<i>C Kerkhof</i> v Brenntag North America et al., Case Bi. 439392-V (Circuit Court for Montgomery County, Maryland)	Deposition
October 26, 2018	<i>A Brower</i> v Johnson and Johnson, Inc. et al., Civil Action File No. 16-EV-005534-E (State Court of Fulton County, State of Georgia)	Deposition
November 15, 2018	<i>T Leavitt</i> v Johnson and Johnson Inc., et al., Case No. RG17882401, (Superior Court of the State of California for the County of Alameda)	Deposition
November 30, 2018	<i>S Pipes</i> v American Honda Motor Co., Inc., et al., Case No. CJ-2017-3487, (District Court of Oklahoma County, State of Oklahoma)	Deposition

December 14, 2018	<i>D Henson</i> v Colgate-Palmolive Company, et al., Case No. BC702253, (Superior Court of the State of California for the County of Los Angeles)	Deposition
December 19, 2018	<i>P Fong</i> v Johnson & Johnson, et al., Case No. JCCP 4674, (Superior Court of the State of California for the County of Los Angeles)	Deposition
January 2, 2019	<i>J Lee</i> v A.W. Chesterton Company, et al., Case No. FSCS050176, (Superior Court of the State of California for the County of Solano)	Deposition
January 7, 2019	<i>R Blinkinsop</i> v Albertsons Companies, Inc., et al., Case No. BC677764, (Superior Court of the State of California for the County of Los Angeles)	Deposition
January 23, 2019	<i>G Koretoff</i> v Arkema, Inc., et al., Case No. BC656506, (Superior Court of the State of California for the County of Los Angeles)	Deposition
February 15, 2019	<i>D Rininger</i> v Hollingsworth & Vose Company, et al., Case No. AC-2014-11-5256, (Court of Common Pleas, Summit County, Ohio)	Deposition

EXHIBIT B

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EXHIBIT C

CURRICULUM VITAE

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Charlotte, VT 05445

Education

MS - University of Vermont, Physiology & Biophysics, 1970
PhD - University of Vermont, Cell Biology, 1977

Fields of Specialization

Environmental toxicology, pathogenesis of mesothelioma, epithelial cell differentiation, chemical and physical carcinogenesis and cell injury, pulmonary fibrosis, oxygen free radicals, molecular biology of antioxidant enzymes in lung, signaling pathways in cell injury and survival

Career Appointments/Honors

2017	Elected Fellow to the Vermont Academy of Arts and Sciences, "for her ground-breaking and award-winning research on mesothelioma and other asbestos-induced diseases".
2011	University of Vermont, University Distinguished Professor, in Recognition of Outstanding Contributions to her Discipline (one of less than 10 awards historically at UVM)
2010	University of Vermont College of Medicine, UVM Medical Alumni Association Distinguished Graduate Alumni Award, "for Outstanding Achievements in Research, Education, Public Service and Humanitarianism"
2008	Wagner Award, International Mesothelioma Interest Group Meeting, Amsterdam, NL, for Historic Contributions to Mesothelioma Research
2007	American Thoracic Society Career Achievement Recognition Award for Scientific Accomplishments
2004	Alumni Achievement Award, University of Vermont College of Medicine
1995 - 2013	Director, Environmental Pathology Program, University of Vermont College of Medicine
1995 - 1998	Program Leader, Cell Signaling and Growth Control Research Program, Vermont Cancer Center
1992 -	Professor, Department of Pathology, University of Vermont College of Medicine
1989 -	Adjunct Faculty Member, <i>In Vitro</i> Cell Biology and Biotechnology Program, State University of New York, Plattsburgh, NY
1984 - 1992	Associate Professor, Department of Pathology, University of Vermont College of Medicine
1984 - 1988	Chair, Cell and Molecular Biology Program, University of Vermont College of Medicine
1981 - 1982	First University of Vermont Medical Scholar Award for "outstanding and sustained research and scholarly contributions to both the academic discipline and the life of the University of Vermont"
1980 - 1983	Assistant Professor, Department of Pathology, University of Vermont College of Medicine
1978 - 1980	Research Assistant Professor, Department of Pathology, University of Vermont College of Medicine
1975 - 1977	Research Associate, Department of Pathology, University of Vermont College of Medicine
1973 - 1974	Research Assistant, Department of Pathology, University of Vermont College of Medicine
1970 - 1973	Research Assistant, Institute of Environmental Medicine, New York University, Sterling Forest, NY

1968 - 1970 Research Assistant, Department of Obstetrics and Gynecology, University of Vermont College of Medicine
1968 - 1970 Graduate Student, Physiology and Biophysics, University of Vermont College of Medicine

Editorial Boards

Current:

1998 - American Journal of Respiratory Cell and Molecular Biology
2004 - Particle and Fibre Toxicology
2005 - Current Respiratory Medicine Reviews
2006 - International Journal of COPD
2010 - International Journal of Clinical and Experimental Pathology

Past:

1993 - 2005 Toxicology and Applied Pharmacology
1993 - 2010 Free Radical Biology and Medicine
1996 - 2005 Laboratory Investigation
1996 - 2006 American Journal of Physiology (Lung Cell Molecular Physiology)
2004 - 2006 The International Journal of Biochemistry & Cell Biology
2004 - 2012 American Journal of Pathology

Reviewer (Journals)

American Journal of Physiology: Lung Cell Molecular Physiology
American Journal of Respiratory and Critical Care Medicine
American Review of Respiratory Diseases
American Industrial Hygiene Association Journal
Archives of Biochemistry & Biophysics
Atherosclerosis
Cancer Research
Carcinogenesis
Cell Biology & Toxicology
Cell & Tissue Kinetics
Chemical Research in Toxicology
Chest
Clays and Clay Minerals
Clinical Cancer Research
Clinical Pathology and Pharmacology
Critical Review in Toxicology
Dose Response
Drug and Chemical Toxicology (past section Head of *In Vitro* Toxicology)
Environmental Health Perspectives
Environmental Mutagenesis, Carcinogenesis
Environmental Research
European Journal of Cancer & Clinical Oncology
Experimental Cell Research
Experimental Lung Research
In Vitro Toxicology
Inhalation Toxicology
Journal of the American College of Toxicology
Journal of Biological Chemistry
Journal of Cellular Physiology
Journal of Clinical Investigation
Journal of Clinical and Laboratory Medicine
Journal of Leukocyte Biology
Journal of the National Cancer Institute

Journal of Toxicology and Applied Pharmacology
Lung Cancer
Molecular Medicine
Molecular Cancer Therapeutics
Nanotoxicology
Nature
Nature Nanotechnology
New England Journal of Medicine
New Journal of Chemistry
Nutrition and Cancer
Oncotarget
Regulatory Pharmacology and Toxicology
Risk Analysis
Scanning Electron Microscopy
Science

Appointments on National and International Committees/Panels

Site visit participant and reviewer of grants for National Science Foundation; Environmental Protection Agency; National Cancer Institute; National Heart, Blood and Lung Institute; Member of Special Review Group on Chemoprevention Projects; National Cancer Institute; Study Section on Small Business Innovative Research (SBIR) Grants, NCI; National Science and Engineering Research Council of Canada; Veterans Administration research awards; Medical Research Council of Canada, American Cancer Society; Western Provinces Lung Association Grant Review Committee; Nickel Producers Environmental Research Association; Center for Indoor Air Research Contributor, Surgeon General's Report, "Smoking Related Cancer and Chronic Lung Disease in the Workplace", Special Emphasis Panels (Clinical Sciences) on a regular basis.

National Academy of Sciences Committee on "Non-Occupational Health Risks of Asbestiform Fibers", **1982 - 1983**

Consultant, EPA Scientific Advisory Board for Review of Airborne Asbestos Health Update, **1985**

External Advisory Committee, Stony Brook-Brookhaven Program Project on "Particle Deposition and Clearance by the Lung", **1985**

External Advisory Committee, University of California at Davis, Program "Pulmonary Effects of Environmental Oxidants", **1987 - 1990**

Scientific Advisory Committee, Alternative Approaches to Animal Testing, Proctor & Gamble, Cincinnati, OH, **1988**

Scientific Advisory Committee, Owens-Corning Fiberglas, Toledo, OH, **1988 - 1989; 1999 - 2000**

External Advisory Committee, Asbestos Research, Health Effects Research Institute, Cambridge, MA, October 31 - November 1, **1988**

Literature Review Panel on Asbestos, Health Effects Research Institute, **1990 - 1992**

Chemical Pathology Study Section, NIH, Ad hoc, **1992, 1995**

Member, Human Exposure and Health Effects Grant Review Panel, US Environmental Protection Agency, **1989 - 1993**

Member, NIOSH Board of Scientific Counselors, Fiber Subcommittee, **1989 - 1993**

Pulmonary Diseases Advisory Committee, NHLBI, **1990 - 1994** (Chair, **1994**)

Scientific Advisory Committee for Research Grants (Personnel for Research), American Cancer Society, **1991 - 1994**

Representative of the American Association of Pathology to the FASEB Life Sciences Research Advisory Committee, **1991 - 1994**

Invited guest of the Lung Division to NHLBI Council Meetings, September, **1993, 1994**

American Thoracic Society, Planning Committee, **1994 - 1997**

American Association for Cancer Research, Program Committee (Lung Cancer), **1994**

Co-Chair (with Dr. Gary Hunninghake), NHLBI, Coordination of Special Emphasis Research Panels for the Lung Division, **1994**

Member, US Environmental Protection Agency, Science Advisory Board, Environmental Health Committee, **1986 - 1996**
Assembly on Environmental and Occupational Health, Program Committee, American Thoracic Society (ATS), **1992 - 1996**
Ad Hoc Reviewer of the Laboratory of Human Carcinogenesis, Division of Basic Sciences, National Cancer Institute, September, **1996**
External Advisory Committee, NIEHS Center at Oregon State University, **1996 - (Chair, 2003 - 2004)**
Contributor and Panel Member, *Relevance of the Rat Lung Response to Particle Overload for Human Risk Assessment*, ILSI Risk Science Institute, Washington, DC, **1998**
Council Member, The Oxygen Society, 1995-1999; Chair, Annual Mtg., Washington, DC, November, **1998**
Lung Biology and Pathology Study Section, NIH, July, **1995 - 1999**
American Society of Investigative Pathology, FASEB Program Committee, **1997 - 2000**
Board of Scientific Counselors (Subcommittee on Basic Research), National Cancer Institute, **2000 - 2005**
External Reviewer, Pilot Grant Program, NIEHS Center, Harvard University, **2002**
Parent Program Project Review Committee Member, National Heart, Lung and Blood Institute, **2002 - 2006, currently Ad Hoc member**
Scientific Advisory Board, CIIT Center for Health Research, **1995 - (Chair, 2002 - 2003)**
External Scientific Advisory Committee, EPA Center for Particulate Health Effects, NYU, **2003 - 2005**
Board of Scientific and Policy Advisors, American Council on Science and Health, **2003 -**
External Advisory Committee, NIEHS Center for Molecular Toxicology, Vanderbilt University, Nashville, TN, **2003 -**
External Advisory Committee, Center for Asbestos-Related Diseases (CARD), Libby, Montana, **2003 - (Focus Award, 2006)**
NIEHS Center Overview Committee, **2004**
NIEHS Review Committee: Transitional Investigator Position Awards (TIPS), **2004 -**
NIEHS Superfund grant reviewer, **2005**
Program Committee, American Society for Investigative Pathologists (ASIP), **2004 - 2006**
External Advisory Committee, Center of Biologic Research Excellence (COBRE NIH) in "Lung Biology", Dartmouth Medical College, Hanover, NH, **2004 - 2012**
External Protocol Review Committee, Beryllium BioRepository, Department of Energy, **2006**
Chair, External Advisory Committee, NIEHS Director's Challenge Project on "Genetics of Susceptibility to Hyperoxia Insult", NIEHS, **2006 - 2010**
Advisory Committee, Nano-Interact Project of the European Union, **2006 -**
External Advisory Committee, Department of Environmental and Occupational Health, School of Public Health, University of Pittsburgh, Pittsburgh, PA, **2006 -**
American Society for Investigative Pathology (ASIP), Education Committee, **2007 - 2009**
American Thoracic Society, Research Program and Funding Committee, **2007 - 2008**
Peer Reviewer, NIOSH White Paper: Asbestos and Other Mineral Fibers: A Roadmap for Scientific Research, **2007**
External Reviewer, EPA National Health and Environmental Effects Research Laboratory (NHEERL), Action plan on Libby amphibole asbestos, **2007**
Evaluation and Review Panel (REP), National Mesothelioma Virtual Bank, University of Pittsburgh, **2007 -**
Chair, Special Emphasis Panel, NHLBI: RFA on Targeting Smooth Muscle in Prevention of Asthma, **2009**
Speaker and Participant, Institute of Medicine/National Research Council, Workshop on the NIOSH Research Roadmap on Asbestos Fibers and Other Elongated Mineral Particles, **2009**
External Reviewer, National Center for Environmental Assessment's (NCEA) Technical Qualification Board Review, **2011**
Review Panel, Virtual Consortium for Translational/Transdisciplinary Environment Research Review Meeting, NIEHS, **2011**
Reviewer, AIRC (Associazione Italiana per la Ricerca sul Cancro) research grants, **2011 - 2012, 2014**
Review Panel, International Collaborations in Environmental Health, NIEHS, June **2012**
Reviewer, NIOSH Nanotechnology Research Center (NTRC) FY13 intramural project proposal, November **2012**

Session Co-Chair "Naturally Occurring and Synthetic Fibers including Nanofibers and Nanotubes", Geological Society of America, Northeastern Section Meeting, Bretton Woods, NH, March 17 - 19, **2013**
Organizing Committee, 10th International Meeting on Particle Toxicology, Dusseldorf, Germany, June 4 - 7, **2013**
Scientific Advisory Board, Mesothelioma Applied Research Foundation (MARF), **2013 - 2018**
Editor, Science Quarterly of MARF, **2014**
Chair, Special NIH Review Panel, NHLBI Parent Program Project Study Section, Washington, DC, June 13, **2013**
Chair, Special NIH Review Panel, RFA on Pulmonary Hypertension Phenomics, Bethesda MD, June 17, **2014**
External Advisory Committee, NIEHS Superfund grant on "Asbestos: fate, exposure, remediation, and health effects, University of Pennsylvania, **2014 -**
Ad Hoc Member, Special Emphasis NIH Panel/Scientific Review Group on "Cancer Etiology", Gaithersburg, MD, June 19 - 11, **2015**
Ad Hoc Member, Board of Scientific Counselors, NCI, Internal Review Program, October 28 - 30, **2015**
Organizing Committee, 11th International Meeting on Particle & Fiber Toxicology, Singapore, September **2016**
International Mineralogical Association (IMA) Working Group on Asbestos, **2019**

Invited Participant/Speaker in NIH/EPA Workshops

"Pleural Cell Biology in Health and Disease", NHLBI, October 1 - 2, **1990**
"Neuroendocrine Cells in Pulmonary Biology", NHLBI, September 5 - 6, **1991**
"Research Needs and Opportunities Related to Respiratory Health of Women", NHLBI, January 30 - 31, **1992**
Co-chair, "Environmental Lung Disease: Relationship between Acute Inflammatory Responses to Air Pollutants and Chronic Lung Disease", NHLBI/NIEHS, May 29 - 31, **1991**
Co-chair, "*In Vivo* Cell Biology", NHLBI, June 7 - 8, **1993**
"Pulmonary Complications of Breast Cancer Therapy", NHLBI, September 20, **1993**
"New Approaches to Pulmonary Fibrosis", NHLBI, August 30 - 31, **1994**
Chair, "Genetics and Gene Therapy for the Study of Pulmonary Diseases", NHLBI, September 23 - 24, **1994**
Chair, "Strategies for Interventions in Aging and Age-Related Diseases", NIA, July 14 - 16, **1999**
Training Evaluation Working Group, NIEHS, September 14 - 15, **1999**
Planning Committee and Chair of Working Group, Signal Transduction Workshop, NIEHS, April 11 - 12, **2001**
Working Group on Pulmonary Fibrosis, NHLBI, June 26 - 27, **2001**
Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length, Agency for Toxic Substances and Disease Registry (ATSDR/EPA), New York, NY, October 7 - 9, **2002**
Panel Member and Speaker, EPA Workshop on Asbestos Mechanisms of Toxicity, Chicago, IL, June 12 - 13, **2003**
Working Group member, EPA/ATSDR panel on Libby Asbestos Mine, Libby, MT, August 17 - 19, **2003**
Panel Member/Session Chair: Validation of Causal Relationships in Criteria to Establish Etiology of Human Cancers, Division of Biological Carcinogenesis and Toxicology, National Cancer Institute, December 11 - 12, **2003**
Invited Participant, NHLBI/Cystic Fibrosis Foundation workshop on "Adult Stem Cells, Lung Biology, and Lung Disease", University of Vermont College of Medicine, Burlington, VT, July 25 - 27, **2005**
Invited Working Group Member, NIEHS/NTP Working Group on "Biomarkers for Toxicology Studies", Research Triangle Park, NC, September 20 - 21, **2006**
Invited Expert, National Toxicology Program's (NTP) Report on Carcinogens (RoC) Registry, **2008**
Group Leader, Asbestos: A Science-Based Examination of the Mode of Action of Asbestos, NIEHS/EPA, Research Triangle Park, NC, December 16 - 17, **2009**
Invited Panelist and Lecturer, "Inflammasome Activation from Erionite", Workshop on Erionite, NIEHS, Research Triangle Park, October 12, **2011**
Chair, Special NHLBI Review Panel, "Systems pharmacogenomics of asthma treatment, November 3, **2017**
Planning Committee on "Elongate Mineral Particles: Integrating Terminology and Characterization", National Academies of Science, **2017- 2018**

Societies

Sigma Xi Scientific Honor Society
American Association for Cancer Research
American Thoracic Society
American Society of Investigative Pathology
Pluto Society for Excellence in Pathology Research (University Associates in Pathology)
Women in Cancer Research
Pulmonary Pathology Society
The International Association for the Study of Lung Cancer (IASLC)

University Committees

Animal Care Committee, Given Institute
Admissions Committee for the Medical College
Steering Committee, Cell Biology Program
Admissions Committee, Cell Biology Program
Graduate Education Coordinator for the Department of Pathology
Search Committee for Chair of Pediatrics
Evaluation Committee for Chair of Biochemistry
Senate Committee on Research and Scholarship
Search Committee for Dean, College of Agriculture and Life Sciences
Self-Study Committee on Re-accreditation
Evaluation for Chairman of Pharmacology
Hearing Officer, Office of Affirmative Action
Task Force on Research and Scholarship
Given Asbestos Management Task Force
University of Vermont Faculty Mentorship Program
Graduate Alumni Award Committee

Invitations/Presentations

"Interaction of Crocidolite with the Tracheobronchial Epithelium in Organ Cultures", Proceedings for the Society of Experimental Biology and Medicine, Champlain Division, Stamford, CT, November 15, **1975**
"Long-term Maintenance of Hamster Tracheal Organ Cultures", GAP Workshop on Tissue Culture Models to Study Cystic Fibrosis Lake Placid, NY, October 12 - 14, **1977**
"Interaction of Environmental Particulates with the Tracheobronchial Epithelium", School of Public Health, Harvard University, Boston, MA, January 30, **1978**
"Models of Respiratory Carcinogenesis" Dartmouth Medical School, Hanover, NH, October 15, **1978**
"Organ Culture as a Tool to Study Environmental Carcinogenesis" Workshop on Teaching of Environmental Pathology, Aspen, CO July 29 - August 3, **1979**
Invited Participant, International Workshop on "Effects of Mineral Dusts *In Vitro*", MRC Pneumoconiosis Unit, Cardiff, Wales, September, **1979**
"Comparative Cytotoxicity of Chrysotile and Crocidolite Asbestos in Hamster Tracheal Epithelial Cells", Gordon Conference: Pulmonary Biology: Lung Injury, Colby Sawyer College, New London, NH, August 11 - 15, **1980**
"Interaction of Minerals with Cell Membranes", Clay Minerals Society, Waco, TX, October 5 - 9, **1980**
"Asbestos and Carcinogenesis - Mechanisms of Cellular Injury", Department of Pulmonary Medicine, Yale University, New Haven, CT, January 21, **1981**
"Mechanisms of Asbestos Carcinogenesis", American Health Foundation, Naylor-Dana Institute, Valhalla, NY, January 23, **1981**
Invited Participant, Conference on Epidemiological, Immunological Genetical Aspects of Asbestosis Wroclaw, Poland, March, **1981**
"Studies of Cellular Mechanisms in Asbestos-induced Disease", State University of New York, Department of Health, Division of Laboratories and Research, Albany, NY, June 20, **1981**
Key Note Speaker, "Asbestos-induced Cancers", Annual Meeting of the American Cancer Society, Vermont Division, Montpelier, VT, October 15, **1981**

"Mechanisms of Asbestos-induced Carcinogenesis in Hamster Trachea", 12th Conference on Environmental Toxicology, Dayton, OH, November 3, **1981**

Invited Participant, 2nd International Workshop on "Effects of Mineral Dusts *In Vitro*", NCTR Little Rock, AK, April, **1982**

"Mechanisms of Asbestos and Nonasbestiform Particles and Fibers in Bronchogenic Carcinoma", 4th Annual RMCOEH Occupational and Environmental Health Conference on Health Issues Related to Metal and Nonmetallic Mining, Park City, UT, April 7 - 9, **1982**

"Asbestos - Mechanisms of Cytotoxicity and Carcinogenicity in the Respiratory Tract", School of Public Health, University of California at Berkeley, Berkley, CA, June 11, **1982**

"*In Vitro* Studies Pertaining to Ingested Asbestos", Summary Workshop on Ingested Asbestos, US EPA, Cincinnati, OH, October 13 - 14, **1982**

Session Chairperson and Speaker, "Chemical-induced Injury", International Conference on Beta Cell Injury, Juvenile Diabetes Foundation, Princeton, NJ, October 27 - 30, **1982**

"Alternate Approaches to Animal Testing: Tracheal Organ Culture", Battelle Laboratories, Columbus, OH, March 29, **1983**

"Mechanisms of Asbestos Carcinogenesis", University of South Alabama College of Medicine, Graduate Program in Basic Medical Sciences, Mobile, AL, November 10, **1983**

"Cocarcinogenesis and Tumor Promotion by Particulates and Fibers in the Respiratory Tract", Conference on Tumor Promotion and Enhancement in Human and Experimental Respiratory Tract Carcinogenesis, US EPA, Williamsburg, VA, June 17 - 20, **1984**

"*In Vitro* Studies on Asbestos-induced Carcinogenesis", W. Alton Jones Cell Science Center, Lake Placid, NY, July 17, **1984**

"Mechanisms of Cell Damage and Carcinogenesis by Asbestos", National Institute of Occupational Safety and Health, Morgantown, WV, September 10, **1984**

Member, Organizing Committee, 3rd International Workshop on Effects of Mineral Dusts *In Vitro*, Hochschwarzwald, Germany, September, **1984**

"Cellular Mechanisms of Damage and Carcinogenesis by Asbestos and Polycyclic Aromatic Hydrocarbons", National Institute of Environmental Health Sciences, Research Triangle, NC, January 17, **1985**

"Mechanisms of asbestos-induced toxicity and carcinogenicity" Department of Pathology, State University of New York at Syracuse, Syracuse, NY, March 18, **1985**

"Pathogenesis of asbestos-associated disease "Division of Pulmonary Medicine, Yale University, New Haven, CT, March 27, **1985**

Invited Participant, International Conference on Biological Mechanisms of Occupational Lung Disease Park City, UT, April, **1985**

"Oxygen free radicals in asbestos-induced lung injury" AIR Seminar Series, University of Rochester Medical Center, Rochester, NY, April 30, **1985**

"Role of Active Oxygen Species in Asbestos-associated Toxicity", Fine Particles Symposium, Miami, FL, April 22, **1985**

"*In Vitro* Approaches to Study of Respiratory Tract Cancers", National Institutes of Health, Interagency Collaborative Group on Environmental Carcinogenesis, Bethesda, MD, October 16, **1985**

"Mechanisms of asbestos-associated carcinogenesis", New York University Medical Center, Division of Environmental Medicine, Sterling Forest, NY, October 23, **1985**

"Importance of Fiber Length and Dimension in Asbestos-induced Toxicity and Carcinogenesis", US Army, Department of Toxicology, Aberdeen, MD, December 18, **1985**

Scientific Program Chairman, 37th Annual Meeting of the Tissue Culture Association, Chicago, IL, **1986**

"Mechanisms of Asbestos Carcinogenesis", Session-In-Depth on Mechanisms of Cell-Toxicant Interaction, 37th Annual Meeting of the Tissue Culture Association, Chicago, IL June 7, **1986**

"Oxygen Free Radicals as Causative Factors in Asbestosis", University of Connecticut, Department of Laboratory Medicine, Farmington, CT, June 23, **1986**

"Approaches to Prevention of Asbestos-induced Fibrotic Lung Disease in Rats Using Administration of Polyethylene (PEG)-conjugated Scavengers of Active Oxygen Species", ENZON Conference on "Modified Enzymes in Free Radical Research", Princeton, NJ, July 19, **1986**

Invited Participant, 14th International Cancer Congress, Panel on Experimental and Human Respiratory Tract Carcinogenesis, Budapest, Hungary, August, **1986**

Invited Session Chair, 4th International Conference on Pulmonary Fibrosis, Gothenburg, Sweden, October, **1986**

"Mechanisms of asbestos-induced carcinogenesis," Defense Research Institute, Seminar on "Asbestos Medicine," Boston, MA, November 21, **1986**

"Role of oxygen free radicals in asbestos-induced lung disease," Conference on "Oxygen Radicals and Antioxidants in Cancer and Aging," University of California at Berkeley, Berkeley, CA, February 6 - 7, **1987**

"Mechanisms of Pulmonary Carcinogenesis by Inorganic Particles," Workshop on "Mechanisms and Distributions of Environmental Disease," Montreal, Quebec, Canada, April 28, **1987**

"Asbestos Fibers and Disease," Policy Forum: Asbestos in Commercial Buildings, Urban Land Institute, Washington, DC, June 16, **1987**

Invited Lecturer, British Association of Lung Research Meeting on "Mineral Fibers," Surrey, England, July 13 - 14, **1987**

Invited Session Chair, IARC-WHO Symposium, "Mineral Fibers in the Non-Occupation Environment Lyon, France, September 8 - 10, **1987**

"Mechanisms of Asbestos Fibers in Disease," Symposium on Scientific Advances in Environmental Medicine, New York University Institute of Environmental Medicine, New York, NY, October 29 - 30, **1987**

Scientific Program Chair, NATO-NIH Advanced Research Workshop on Effects of Mineral Dusts *In Vitro*, Sherbrooke, Quebec, Canada, **1988**

Invited Discussant, "Oxygen Radicals in Xenobiotic-induced Tissue Injury", Upjohn - UCLA Symposium on Oxy-Radicals in Molecular Biology and Pathology, Park City, UT, January 24 - 30, **1988**

"Free Radical Mechanisms in Asbestos-induced Diseases, Symposium on Free Radical Mechanisms in Pathogenesis, Annual meeting of the Society of Toxicology, Dallas, TX, February 16 - 19, **1988**

Invited Speaker, BOMA International Asbestos Management Seminar, New York, NY, March 10 - 11, **1988**

Invited Participant, International Symposium on "Biological Interaction of Inhaled Mineral Fibers and Cigarette Smoke," Battelle-Seattle, WA, April 10 - 14, **1988**

"Mechanisms of Cell Damage and Proliferation by Asbestos", W. Alton Jones Cell Science Center, Lake Placid, NY, May 10, **1988**

Invited Participant, Proctor and Gamble Workshop on "Future Directions in Research on Toxicology of the Respiratory Tract", Cincinnati, OH, October 17 - 19, **1988**

"Fibers", meeting on "Biology, Toxicology and Carcinogenesis of the Respiratory Epithelium", Albuquerque, NM, November 14 - 16, **1988**

"Factors Influencing Individual Responses to Asbestos", Symposium on "Health Aspects of Asbestos in Buildings", Energy and Environmental Policy Center, John F. Kennedy School of Government, Harvard University, Cambridge, MA, December 14 - 16, **1988**

"Mechanisms of Asbestos-induced Diseases", Wadsworth Center for Laboratories and Research Scientific Seminar Series, State of New York Department of Health, Albany, NY, January 24, **1989**

Invited Session Chair, 1st International Conference on Health Related Effects of Phyllosilicates, Paris, France, March 16 - 17, **1989**

Invited Session Chair and Speaker, Colloquium Ramazzini International Meeting on "Different Pathogenic Potential of Asbestos Fibers" Ottawa, Ontario, Canada, March 20 - 22, **1989**

"The Medical Case from the Doctor's Standpoint" Asbestos in Buildings: The Laws, the Costs, the Solutions, Law Journal Seminars-Press, New York, NY, April 13 - 14, **1989**

"Asbestos toxicology", Toxicology Update, Current Concepts in Inhalation Toxicology, Johns Hopkins University, Baltimore, MD, April 24 - 26, **1989**

Session Leader/Invited Speaker, NIEHS Workshop on Research Needs in Fiber Toxicology, Research Triangle Park, NC, July 10 - 12, **1989**

"Antioxidant Enzyme Defense Mechanisms in Asbestos-related Lung Injury", Chicago Lung Association Conference on Occupational Lung Disease, Chicago IL, October 19 - 22, **1989**

"Asbestos: Scientific Developments and Public Policy", American Industrial Hygiene Association, Meriden, CT, March 14, **1990**

"Mechanisms of Asbestos-induced Lung Disease", Department of Pathology, Mount Sinai School of Medicine, New York, NY, March 19, **1990**

"Role of Oxy-radicals in Rodent Cells", Cold Spring Harbor Conference on Mechanisms of Fiber Cytotoxicity and Carcinogenesis, Banbury Conference Center, Long Island, NY, March 20 - 22, **1990**

"Active Oxygen Species in Asbestos-induced Cell Damage and Disease", Symposium on "Free Radical Mechanisms of Tissue Injury", Annual meeting of the American Chemical Society, Boston, MA, April 22, **1990**

"Mechanisms of Asbestos-related Diseases", Society for Risk Analysis', Forum on Risk of Indoor (Asbestos) Building Materials, Washington, DC, May 7 - 8, **1990**

"Mechanisms of Asbestos-induced Lung Disease", Symposium on "Particle-Lung Interactions: Overload Related Phenomena", Rochester, NY, May 17- 18, **1990**

"Asbestos: Scientific Developments", Clinical Research Institute of Montreal, Montreal, QC, Canada, May 22, **1990**

"Asbestos: An Overview on Mechanisms of Action in the Causation of Lung Diseases", Symposium on "Exogenous and Endogenous Factors as Major Cancer Risks in Carcinogenesis", 81st Annual Meeting of the American Association of Cancer Research, Washington, DC, May 26, **1990**

Invited Speaker, International Meeting on "Free Radicals in Health and Disease" Johannesburg, South Africa, July 18 - 20, **1990**

"Health Effects of Low Level Exposure", Workshop on Asbestos in Buildings, Canadian Centre for Occupational Health and Safety, Laval, Quebec, Canada, September 11, **1990**

"Recent Information on Potential Health Risks from Exposure to Asbestos", American Association of School Administrators "I Care" Conference, Hyatt Regency on Capitol Hill, Washington, DC, September 13, **1990**

"Risks from Asbestos Exposure" Society for Risk Analysis Annual Meeting, New Orleans, LA, October 7, **1990**

Organizing Committee, 6th International Colloquium on Pulmonary Fibrosis, Stowe, VT, October 14 -17, **1990**

Scientific Chair, Session on "Evidence for Mechanisms from Cell Culture Studies" NATO Meeting on "Mechanisms of Fibre Carcinogenesis", Albuquerque, NM, October 22 - 25, **1990**

"The Risks of Asbestos in Buildings: The Need for National Policy", Brookings Institute, Washington, DC, November 7, **1990**

Visiting Pulmonary Scholar sponsored by Burroughs Wellcome; the Chemical Industry Institute of Toxicology; Duke University; the US Environmental Protection Agency; the National Institute of Environmental Health Sciences; North Carolina State University Veterinary School and the University of North Carolina, Raleigh, NC, February 5 - 7, **1991**

"Asbestos and Lung Disease", Grand Rounds, St. Luke's/Roosevelt Hospital, Department of Medicine, New York, NY, February 13, **1991**

"Oxidant-induced Cell Injury by Asbestos", Department of Pathology, Baylor College of Medicine, Houston, TX, March 21, **1991**

"Molecular Biology of Asbestos Interactions with Tracheal Epithelial Cells and Lung Fibroblasts", Wayne State University, Detroit, MI, April 8, **1991**

"Oxidants, Antioxidants, and Asbestos-induced Lung Disease", Institut Lady Davis de Recherches Medicales, Montreal, Quebec, Canada, April 16, **1991**

"Oxidants, Antioxidants and Asbestos-related Lung Disease", American Health Foundation, Valhalla, NY, May 9, **1991**

Chair and Session Summarizer, "Mechanisms of Asbestos-induced Lung Disease", American Thoracic Society, American Lung Association Annual Meeting, Los Angeles, CA, May 14, **1991**

Invited Speaker, 10th International Symposium for Society of Toxicologic Pathologists, Pulmonary Toxicologic Pathology, "Mechanisms of Asbestos-induced Lung Injury in a Rat Inhalation Model of Disease", Monterey, CA, June 4, **1991**

"Oxidant Injury and Asbestos-induced Lung Disease", National Institute of Environmental Health Sciences, Research Triangle Park, NC, September 3, **1991**

Session Chair and Invited Lecturer, "Oxidants and Enzyme Induction", 4th International Conference on Environmental Lung Disease: At Home, At Work: Mechanisms, Manifestations and Management, Montreal, Quebec, Canada, September 25 - 28, **1991**

Scientific Program Committee, American College of Chest Physicians (ACCP) 4th International Conference on Environmental Lung Disease, Montreal, Quebec, Canada, September 24 - 26, **1991**

Session Scientific Chair, "Epidemiology of Malignant Mesothelioma", International Conference on "Mesothelial Cell and Mesothelioma: Past, Present and Future", Paris, France, September 30 - October 2, **1991**

"Mechanisms of Asbestos-induced Lung Cancer and Mesothelioma", American Society of Clinical Oncology, Educational Workshop, Miami, FL, November 8, **1991**

Invited Participant and Rapporteur, Workshop on "Approaches to Evaluating the Toxicity and Carcinogenicity of Man-made Fibers", sponsored by Duke University Center for Extrapolation Modeling, Thermal Insulation Manufacturers Association and US Environmental Protection Agency, Durham, NC, November 11 - 13, **1991**

"Approaches to Testing Synthetic Fibers for Disease Potential", Toxicology Division, Dow Chemical Company, Midland, MI, January 20, **1992**

"Biochemical Mechanisms in Asbestos-related Carcinogenesis and Fibrosis", Department of Biochemistry, Loyola University of Chicago, IL, February 10, **1992**

"Asbestos", Invited Speaker at Symposium on "How Well does Environmental Policy Track Science", Annual meeting of the American Association for Advancement of Science, Chicago, IL, February 11, **1992**

Invited Speaker, "Health Effects of Fibrous Materials", Workshop on Interaction of Glass Surfaces with Chemical and Biological Environments, NSF/University Center for Glass Research, Bethesda, MD, March 5 - 6, **1992**

Plenary Lecturer, 2nd International Meeting on "Free Radicals in Inflammation", Society for Rheumatology, Inflammation, and Free Radical Research, Cape Town, South Africa, March 22 - 26, **1992**

Co-chair and Presenter, Mini-symposium: "Adaptive Responses to Injury", American Association of Pathology, FASEB Meeting, April 9, **1992**

Invited Speaker, "Mechanisms of Asbestos-induced Lung Disease and Preventive Approaches", National Center of Occupational Health, Johannesburg, South Africa, March 28, **1992**

Invited Speaker, "Mechanisms of Asbestos-induced Free Radical Production", Mobil Environmental Technical Center, Princeton, NJ, April 27, **1992**

Invited Speaker, "Effects of Asbestos and Free Radicals on Cellular Proliferation", National Cancer Institute Division of Experimental Pathology, National Institutes of Health, Bethesda, MD, May 7, **1992**

Invited Speaker, "Cancer Risks of Asbestos", Symposium on Risk Assessment of Carcinogens in the Workplace and Environment, Annual meeting of the American College of Occupational Medicine, Washington, DC, May 8, **1992**

"Sensitivity of Human Mesothelial Cells to asbestos and Oxidants", Symposium on "Pleural Disease", American Thoracic Society-American Lung Association International Conference, Miami, FL, May 18, **1992**

"Mechanisms of Asbestos Toxicity and Health Risks", American Society of Testing Materials (ASTM) EPA workshop, Johnson VT, July 12 - 14, **1992**

Scientific Chair, Session on "*In Vitro* Assessment of Biopersistence", WHO-IARC Meeting, on "Biopersistence of Respirable Synthetic Fibres and Minerals", Lyon France, September 7 - 9, **1992**

Invited Plenary Speaker, "Asbestos-recent Scientific Developments", Joint Scientific Session of the Pennsylvania and New Jersey Thoracic Societies and the Eastern Division of the ATS, 100th Anniversary, Philadelphia, PA, September 11 - 12, **1992**

Invited Faculty, Law Institutes Program on Asbestos Medicine "What Do Animal Inhalation Experiments Tell Us About Human Disease?" Defense Research Institute, Chicago, IL, October **1992**

"Molecular Regulation of Cell Proliferation by Asbestos", Department of Biochemistry and Cell Biology, Albany Medical College, Albany, NY, February 1, **1993**

Invited Speaker, 4th International Life Sciences Institute (ILSI) Symposium "Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract", Hannover, Germany, February 28, **1993**

Invited Session Speaker, "Pathology of Lung Injury", American Society for Investigative Pathology, FASEB meetings, New Orleans, LA, March 31, **1993**

Invited Colloquium Participant, International Centre for Scientific Ecology, Paris, France, May 10, **1993**

Member, Advisory Committee, International Meeting on "Oxygen Radical and Lung Injury" NIOSH-NIH, Morgantown, WV, August 29 - September 2, **1993**

Distinguished Professor Lectureship, Jefferson Medical College, Division of Environmental Medicine and Toxicology, Philadelphia, PA, April 28 - 29, **1993**

"Molecular Mechanisms of Asbestos-induced Lung Disease", Seminar series on Pulmonary Biology and Medicine, MD Hershey Medical Center, Penn State University, Hershey, PA, May 7, **1993**

"Protooncogene Induction by Asbestos", 2nd International Mesothelioma Workshop, San Francisco, CA, May 15, **1993**

Session Co-chair and Invited Speaker, "Tissue Structural Cells as Effectors of Response to Inhaled Environmental and Occupational Pollutants", American Thoracic Society/American Lung Association International Conference, San Francisco, CA, May 16 - 19, **1993**

Invited Speaker, "Molecular Mechanisms of Cell Proliferation and Carcinogenesis by Asbestos", Center for Radiological Research, College of Physicians and Surgeons of Columbia University, New York, NY, July 14, **1993**

Invited Plenary Speaker, "The Toxicology of Serpentine and Amphibole Asbestos", American Institute of Chemists/American Chemical Society Annual Meeting, 70th National Meeting, Chicago, IL, August 24, **1993**

Invited Speaker and Session Chair, Symposium on "Cell Signaling and the Molecular Stress Responses", Lake Placid, NY, September 23 - 26, **1993**

"Mechanisms of Asbestos-induced Lung Disease", Division of Pulmonary Medicine, Department of Internal Medicine, Yale University, New Haven, CT, September 30, **1993**

Invited Speaker, International Symposium on "Coal Dust-induced Respiratory Disorders", Maastricht, The Netherlands, October 8, **1993**

Scientific Organizing Committee, 5th International Workshop on Effects of Mineral Dusts *In Vitro*, Creteil, France, October 11 - 13, **1993**

Co-convenor, Symposium, "Health Effects of Mineral Dusts", Mineralogical Society of America, Nantucket, MA, October 22 - 24, **1993**

Invited Speaker, Workshop on "Health Risks Associated with Chrysotile Asbestos", International Commission on Environmental Health, Jersey, Channel Islands, Great Britain, November 14 - 17, **1993**

"Molecular Mechanisms of Asbestos-induced Diseases", Pharmacology and Toxicology Seminar Series, Dartmouth-Hitchcock Medical Center, Hanover, NH, January 19, **1994**

Invited Faculty, Workshop on "Talc: Consumer Uses and Health Perspectives", International Society of Regulatory Toxicology and Pharmacology, FDA, National Institutes of Health, Bethesda, MD January 31 - February 1, **1994**

Invited Speaker, Gordon Conference on "Oxygen Radicals and Biology", Ventura, CA, February 6 - 11, **1994**

Invited Speaker and Session Chair, International Conference on "Crystalline Silica", Baltimore, MD, April 18 - 20, **1994**

Invited Speaker, Wyeth Ayerst Drug Safety Symposium on "Modern Trends in Safety Assessment of Drugs", Chazy, NY May 9, **1994**

"Molecular Mechanisms of Asbestos-induced Lung Diseases", Toxicology Scholars Colloquium, University of Connecticut at Storrs, Center for Biochemical Toxicology, Storrs, CT, May 12 - 13, **1994**

Session Chair, "Pneumoconiosis: Basic Mechanisms", American Thoracic Society/American Lung Association 1994 International Meeting, Boston, MA, May 23, **1994**

Session Co-Chair and Presenter, Symposium on "Transmembrane Signaling and Intracellular Regulation Mechanisms", American Thoracic Society/American Lung Association, 1994 International Meeting, Boston, MA, May 24, **1994**

Invited Speaker, Symposium on "Mesothelioma and Mesothelioma Cells", American Thoracic Society/American Lung Association 1994 International Meeting, Boston, MA, May 24, **1994**

Elected Member, Pluto Club (Honorary Society for Investigative Pathologists), **1994**

"Molecular Mechanisms of Asbestos-Induced Disease", Sealy Center for Molecular Biology, University of Texas at Galveston, Galveston, TX, October 4, **1994**

"Molecular Mechanisms of Asbestos Interactions with Cells", Pulmonary Division, University of Texas at Houston, Houston, TX, October 5, **1994**

Invited Speaker, "Inhalation Models to Explore Mechanisms, Prevention and Treatment of Pulmonary Fibrosis", Wyeth Ayerst Scientific Symposium on Pharmaceutical Aspects of Drug Delivery to the Lung, State University of New York at Plattsburgh, Plattsburgh, NY, October 11, **1994**

Invited Speaker, Postgraduate course on "Cellular Oxidants: Production and Consequences", Queenstown, New Zealand, November 1 - 3, **1994**

Invited Symposium Speaker and Session Chair, VIIth International Meeting of the Society for Free Radical Research, Sydney, Australia, November 7 - 11, **1994**

Invited Speaker, 5th International Life Sciences Institute (ILSI) Symposium, "Correlations Between *In Vitro* and *In Vivo* Investigations in Inhalation Toxicology", Hannover, Germany, February 20 - 24, **1995**

Invited Plenary Lecturer, 5th International Conference on "Environmental and Occupational Disease", American College of Chest Physicians, Orlando, FL, March 2 - 5, **1995**

Invited Plenary Lecturer, "Role of Reactive Oxygen and Nitrogen Species in Cell Signaling and Proliferation by Asbestos, 43rd Annual Meeting of the Radiation Research Society, San Jose, CA, April 1 - 6, **1995**

Invited Session Chair and Guest, "Meet the Researchers", Pulmonary Pathobiology Subsection, Experimental Biology '95, Atlanta, GA, April 9 - 13, **1995**

Invited Lecturer, "An Update on Asbestos", Robert Wood Medical Institute, Rutgers University, Piscataway, NJ, May 11, **1995**

Invited Speaker and Session Chair, American Thoracic Society Annual Meeting, Miami, FL, May 20 - 24, **1995**

Invited Speaker, 3rd International Mesothelioma Conference, Creteil, France, September 12 - 15, **1995**

Invited Speaker, British Association for Lung Research, "Fibres, Particles and the Lung: New Perspectives", Edinburgh, Scotland, September 11 - 12, **1995**

Invited Speaker, Symposium on "Health Effects of Fibrous Minerals Used in Industry Excluding Asbestos", Sydney Australia October 30 - 31, **1995**

Invited Speaker, Keystone Symposium on "Oxidant Stress: from Molecules to Man", Santa Fe, NM, January 8 - 14, **1996**

Invited Participant, Workshop on "Mechanisms of Fibre Carcinogenesis", IARC, Lyon, France, January 9 - 11, **1996**

Invited Session Chair, Gordon Conference on "Oxygen Radicals and Biology", Ventura, CA, February 14 - 19, **1996**

Invited Lecturer, Center for Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ, April 4, **1996**

Session Chair and Invited Speaker, Annual Meeting of the American Thoracic Society, New Orleans, LA, May 10 - 15, **1996**

Invited Plenary Lecturer, Organizing Committee and Editorial Board, 6th International Meeting on "Toxicology of Natural and Man-made Fibrous and Non-fibrous Particles", Lake Placid, NY, September 6 - 19, **1996**

Invited Lecturer, Short Course on "Minerals and Health", Institute of Mineralogy and Petrography, University of Fribourg, Switzerland, October 7 - 11, **1996**

Invited Speaker, Oxygen Society Meeting '96, Miami Beach, FL, November 21 - 25, **1996**

Invited Symposium Speaker, Society of Toxicology Annual Meeting, Cincinnati, OH, March 9 - 12, **1997**

Organizer and Chair, Symposium on "Oxidative Mechanisms of Cell Signaling and Repair in Disease", American Society for Investigative Pathology, Experimental Biology '97, New Orleans, LA, April 6 - 9, **1997**

Organizer and Chair, Trends in Experimental Pathology Symposium, "New Developments in Cell Imaging Techniques for Detection of Cell Injury and Disease", American Society for Investigative Pathology, Experimental Biology '97, New Orleans, LA, April 6 - 9, **1997**

Organizer, Workshop on "Environmental Pathology: New Directions and Opportunities, American Society for Investigative Pathology, Experimental Biology '97, New Orleans, LA, April 6 - 9, **1997**

Invited Lecturer and Honorary Membership Award, The Oxygen Society of Greater Washington, DC, Inc., Annual Meeting, Washington, DC, June 10, **1997**

Invited Session Chair, Cell Viability and Death, XIXth Annual Meeting, International Society for Heart Research, Vancouver, BC, Canada, July 23 - 27, **1997**

Scientific Organizing Committee and Session Chair, 2nd International Conference on Oxygen/Nitrogen Radicals and Cellular Injury, Durham, NC, September 7 - 10, **1997**

Invited Contributor and Session Chair, International Workshop on "Health Effects of Chrysotile Asbestos: Contribution of Science to Risk Management Decisions", Montreal, QC, Canada, September 14 - 16, **1997**

Invited Lecturer, Yale University Symposium on Pulmonary Biology and Environmental Lung Disease, New Haven, CT, October 22, **1997**

Invited Symposium Speaker, Annual Meeting of the Society for Gerontology Research, Cincinnati, OH, November 12 - 17, **1997**

Outstanding Volunteer Contribution Award, The Oxygen Society, Washington, DC, **1998**

Invited Speaker, University of California at Davis, Center for Comparative Respiratory Biology and Medicine, Pulmonary Seminar Series, "Cell Signaling Cascades in Oxidant-induced Lung Injury and Apoptosis" Davis, CA, May 1, **1998**

Invited Speaker, Columbia University; Division of Environmental Health Sciences: "Cell Signaling Events Regulating Apoptosis and Proliferation by Oxidant Stresses in Mesothelial and Pulmonary Epithelial Cells", May 13, **1998**

Invited Speaker, Wayne State University, NIEHS Center Seminar Series: "Cell Signaling by Oxidant Stresses in Lung", Detroit, MI, May 14, **1998**

Invited Speaker, University of Rochester Division of Environmental Health Sciences: "Cell Signaling by Minerals and Oxidants in Environmental Lung Disease", Rochester, NY, May 21, **1998**

Invited Speaker, University of Pennsylvania, "Cell Signaling Mechanisms in Environmental Lung Disease", Philadelphia, PA, September 25, **1998**

Invited Speaker, Pleura 1998: Medical Thoracoscopy - Mesothelioma", "Mechanisms of Asbestos Pathogenesis", Brescia, Italy, October 15 - 16, **1998**

Program Chair, Oxygen '98, Annual Meeting of the Oxygen Society, Washington, DC, November 19 - 23, **1998**

Faculty Member and Speaker, "Mechanisms of Asbestos Carcinogenesis", International Conference on Malignant Pleural Mesothelioma", Lignano, Italy, March 18 - 19, **1999**

Invited Speaker, NIEHS/NHLBI "Apoptosis and Growth Factors/Signal Transduction Pathways: Basic Biology and Toxicology", Raleigh, NC, April 19 - 21, **1999**

Invited Speaker, Department of Environmental Health, Harvard School of Public Health, "Cell Signaling by Environmental Particulates", Boston, MA, May 18, **1999**

Co-leader (with Mark Van Baalen and Carl Francis, Harvard University), "Mineralogy, Petrology and Health Issues at the Ultrametric Complex, Belvidere Mountain, VT", New England Intercollegiate Geological Conference, Burlington, VT, October 1 - 4, **1999**

Keynote Speaker, "Fibre-induced Carcinogenesis", 5th International Mesothelioma Interest Group (IMIG) Meeting, Manchester, England, October 5 - 8, **1999**

Invited Speaker, Symposium on "Asbestos at the End of the Century: Basic Science for Substitutes, Removal and Therapies", Torino, Italy, October 11, **1999**

Scientific Organizing Committee and Invited Speaker, "Cell Signaling by Fibres", 7th International Meeting on Particle Toxicology, Maastricht, The Netherlands, October 14 - 17, **1999**

Invited Speaker, Department of Cell and Molecular Biology, Loyola University Chicago, "Cell Signaling in Asbestos and Silica-Induced Lung and Pleural Disease", Chicago, IL, April 7, **2000**

Scientific Organizing Committee, International Conference on Basic and Clinical Aspects of Cell Cycle Control, Siena, Italy, May 29 - 30, **2000**

Session Chair and Speaker, "Fibrosis - Inflammation, Oxidants and Cytokines", Gordon Conference on Mechanisms of Toxicity, Plymouth State College, Plymouth, NH, July 23 - 28, **2000**

Invited Speaker and Session Chair, British Association for Lung Research, Edinburgh, Scotland, September 6 - 8, **2000**

Scientific Organizing Committee, International Conference on Environmental and Occupational Respiratory Disease, Lucknow, India, October 29 - November 2, **2000**

Session Co-chair, "Lung Epithelial Signaling by Particles and Fibers", Experimental Biology Meetings, Orlando, FL, April 12, **2001**

Faculty and Panel Member, "Malignant Mesothelioma - Therapeutic Options and Role of SV40: An Update", Chicago, IL, April 20 - 21, **2001**

Plenary Speaker, "Reactive Oxygen Species in Lung Injury and Carcinogenesis", 8th Annual Meeting of the Oxygen Society, Raleigh, NC, November 15 - 19, **2001**

Invited Speaker, "Cell Signaling by Oxidative Stress and Inhaled Particles", Johns Hopkins School of Public Health, Baltimore, MD, March 15, **2002**

Scientific Organizing Committee and Invited Speaker, 3rd International Symposium on Reactive Oxygen/Nitrogen Species in Cell Injury and Disease, NIOSH, Morgantown, WV, June 1 - 6, **2002**

Invited Participant and Speaker, 12th International Colloquium on Pulmonary Fibrosis, Geneva, Switzerland, October 7 - 9, **2002**

Invited Speaker, 1st Annual Pittsburgh International Lung Conference: Pulmonary Fibrosis: Bench to Bedside, Pittsburgh, PA, October 12 - 15, **2002**

Invited Speaker and Session Chair, 6th International Mesothelioma Group Meeting, Perth, Australia, December 1 - 4, **2002**

Invited Speaker, International Belle Conference on "Non-linear Dose Response Relationships in Biology, Toxicology, and Medicine, University of Massachusetts at Amherst, MA, May 28 - 30, **2003**

Invited Speaker, 1st International Conference on Molecular Research in Environmental Medicine: "Cell Signaling Pathways in Responses to Particles and Fibers", Dusseldorf, Germany, March 18 - 21, **2004**

Invited Speaker, 7th Meeting of the International Mesothelioma Interest Group (IMIG): "Asbestos-induced Carcinogenic Alterations", Brescia, Italy, June 24 - 26, **2004**

Invited Speaker, British Association for Lung Research, BALR Annual Summer Conference: "Cell Signaling Pathways in Pulmonary Toxicity", University of Leicester, England, September 13 - 15, **2004**

Invited Speaker and Faculty Member, 1st International Symposium on Malignant Mesothelioma: "Pathogenesis and Molecular Biology of Mesothelioma", Nevada Cancer Research Center, Las Vegas, NV, October 14 - 16, **2004**

Faculty, Society of Free Radical Biology and Medicine Annual Meeting, Workshop on "Negotiating for Success", St. Thomas, VI, November, **2004**

Session Chair, Society of Free Radical Biology and Medicine, 11th Annual Meeting, "Free Radical Toxicity and Clinical Implications", November, **2004**

Invited Speaker, Experimental Biology 2005, Session on "Environmental Toxicology, Modulation of Cell Signaling Pathways for Control of Cell Proliferation and Transformation by Asbestos", San Diego, CA, April 4, **2005**

Invited Speaker, Workshop on Directions and Needs in Asbestos Research: New Insights, "Intervention of Asbestos-associated Cell Signaling: Pathways in Mesothelioma", University of Montana at Missoula, Missoula, MT, July 28 - 29, **2005**

Invited Speaker, Annual Meeting of the Oxygen Club of California and the University of Torino: "Oxidant-induced Signaling Pathways and Chemoresistance in Asbestos-induced Mesotheliomas", Alba, Italy, September 7 - 10, **2005** (*could not attend due to family emergency*)

Invited Speaker, "Properties of Asbestos Involved in Mechanisms of Action Leading to Mesothelioma" Institute of Medicine: Asbestos: Selected Health Effects, National Academy of Sciences, Washington, DC, October 5, **2005**

Program Chair, 8th International Meeting on "Mechanisms of Action of Inhaled Particles and Nanoparticles", Research Triangle Park, NC, October 26 - 28, **2005**

Invited Speaker, Department of Thoracic Surgery, "Inhibition of Cell Signaling Pathways in Mesothelioma", Brigham and Women's Hospital, Boston, MA, December 9, **2005**

Invited Speaker, "Screening Assays for Cell Signaling by Particles", 1st International Conference on "Nanotechnology: Biomedical Aspects", Miami, FL, January 30 - February 3, **2006**

Session Chair, Experimental Biology 2006 Symposium on "Molecular and Cellular Basis of Disease: Redox Mediated Diseases, San Francisco, CA, April 4, **2006**

Invited Speaker, "Protein Kinase C Signaling by Asbestos is Critical to Cell Injury, Transcription of Matrix Metalloproteinases and Pulmonary Fibrosis", Department of Pathobiology, Brown University, Providence, RI, May 4, **2006**

Invited Speaker, "Cell Signaling in Mesothelioma", 8th International Conference of the International Mesothelioma Interest Group, Chicago, IL, October 19, **2006**

Faculty Member, "Mechanisms of Mesothelioma", Mesothelioma Applied Research Foundation, Chicago, IL, October 20, **2006**

Program Committee Member and Session Co-Chair, "Physiological Genomics and Proteomics of Lung Disease", American Physiological Society Conference, Fort Lauderdale, FL, November 2 - 5, **2006**

Invited Speaker, "Cell Signaling in Asbestos-Related Diseases", Symposium on "Interactions among Infectious Agents, Environmental Carcinogens & Genetics in Human Cancer Development", John A. Burns School of Medicine and Cancer Center of Hawaii, Honolulu, Hawaii, February 16, **2007**

Invited Speaker, "Oxidant Injury in Lung Disease", Gordon Conference on "Oxidative Stress in Disease", Ventura, CA, March 11 - 15, **2007**

Invited Participant, International Council on Nanotechnology Conference "Towards Predicting Nano-Bio Interactions, Zurich, Switzerland, June 5 - 7, **2007** (*declined due to schedule conflict*)

Invited Speaker, "Gene Profiling and Approaches for Therapy of Mesothelioma Using Nanoporous Spheres", ESF-EMBO Symposium on Probing Interactions between Nanoparticles, Biomaterials and Biological Systems - Alternative Approaches to Bio- and Nano-toxicity, Sant Feliu de Guixols, Spain, November 3 - 8, **2007**

Plenary Speaker, "Asbestos and Cell Signaling", 1st Asian Conference on Environmental Mutagens and 36th Annual Meeting of the Japanese Environmental Mutagen Society, Kitakyushu, Japan, November 29 - 30, **2007**

Organizing Committee, 9th International Conference on Particles: Risks and Opportunities, Cape Town, South Africa, September 2 - 5, **2008**

Faculty and Invited Session Chair, 9th International Conference of the International Mesothelioma Interest Group, Amsterdam, The Netherlands, September 26 - 28, **2008**

Invited Speaker, "Current Perspectives on the Pathogenesis of Mesothelioma", XXVIIth International Academy of Pathology Congress, Athens, Greece, October 12 - 17, **2008**

Invited Speaker, "Microparticles for Release of Chemotherapeutic Drugs and si Constructs in Therapy of Mesotheliomas", 2nd NIH Mesothelioma Conference, Washington, DC, March 6, **2009**

Invited Speaker, "Cell Signaling and Therapies for Mesothelioma", Lung Biology Group, Dartmouth Medical School, Hanover, NH, May 6, **2009**

Invited Speaker, "Use of *In Vitro* and Inhalation Models for Assessment of Nanoparticle Effects on Lung Cells", VIIth World Congress on Alternatives and Animal Use in the Life Science, Rome, Italy, August 30 - September 3, **2009**

Invited Speaker, "The Inflammasome in Asbestos-related Diseases", 4th International Conference on Oxidative/Nitrosative Stress and Disease, New York Academy of Sciences, New York, NY, October 28 - 30, **2009**

Speaker, "Targeting the Inflammasome in Mesothelioma Using Anakinra", International Symposium on Malignant Mesothelioma 2010, Mesothelioma Applied Research Foundation (MARF), Washington, DC, June 10 - 12, **2010**

Invited Speaker, "Inflammation and Asbestos-induced Diseases", Annual Meeting of the American Chemical Society, Boston, MA, August 25, **2010**

Invited Speaker, "Chronic Inflammation and Mesothelioma", American Association of Cancer Research/ American Chemical Society Conference on Chemistry and Cancer Research: The Biological Chemistry of Inflammation as a Cause of Cancer, January 30 - February 2, **2011**

Invited Speaker, "Targeting the Inflammasome in Asbestos-related Diseases", 50th Annual Meeting of the Society of Toxicology, Washington, DC, March 13 - 15, **2011**

Invited Presenter, 1st Annual Libby Amphibole Symposium, October 13 - 14, **2011**

Invited Session Chair and Speaker, "Dose Response Molecular Responses to Asbestos and Silica in Human Lung Cells", 11th Annual International Conference on Dose-Response 2012: Implications for Toxicology, Medicine and Risk Assessment, University of Massachusetts Amherst, Amherst, MA, April 24 - 25, **2012**

Invited Presenter and Session Chair, "ERK Signaling Pathways in Mesothelioma", 11th International Conference of the International Mesothelioma Interest Group, Boston, MA, September 11 - 14, **2012**

Invited Presenter and Panel Member, 2nd Annual Libby Amphibole Symposium, October 12, **2012**

Invited Presenter, Medalist lecture on "Cell Signaling Pathways in Mesothelioma", 12th International Conference of the International Mesothelioma Interest Group, Cape Town, South Africa, October 21 - 24, **2014** (*could not attend due to prior UVM commitment*)

Invited Speaker and Rapporteur, "Mechanistic Studies of EMPs: Cell Cultures, Organ Cultures and Beyond?" The Monticello Conference, Charlottesville, VA, October 16 - 19, **2017**

Invited Speaker and Moderator, "Asbestos in Talc", The Joint Institute of Food Safety and Applied Nutrition (JIFSAN), FDA, University of Maryland, MD, November 28, **2018**

Refereed Manuscripts*, Book Chapters, Monographs and Editorials (*peer-reviewed)

1. *Sivak A, Mossman BT, and Van Duuren BL: Activation of cell membrane enzymes in the stimulation of cell division. *Biochem Biophys Res Comm* 46(2):605-609, **1972** PMID: 4333422

2. *Mossman BT, Gray MJ, Silberman L, and Lipson RL: Identification of neoplastic versus normal cells in human cervical cell culture. *Am J Obstet Gynecol* 43(5):635-639, **1974** PMID: 4595695
3. Mossman BT and Craighead JE: Topical application of polycyclic hydrocarbons to differentiated respiratory epithelium in long-term organ cultures. In: Experimental Lung Cancer, (E Karbe and JF Park, eds.), Springer-Verlag, Berlin, Germany, 514-520, **1974**
4. *Mossman BT and Craighead JE: Long-term maintenance of differentiated respiratory epithelium in organ culture. I. Medium composition. *Proc Soc Exp Biol Med* 149(1):227-233, **1975** PMID: 1144432
5. *Mossman BT, Ley BW, and Craighead JE: Squamous metaplasia of the tracheal epithelium in organ culture. I. Effects of hydrocortisone and β -retinyl acetate. *Exp Mol Pathol* 24(3):405-414, **1976** PMID: 1278337
6. *Mossman BT, Kessler JB, Ley BW, and Craighead JE: Interaction of crocidolite asbestos with hamster respiratory mucosa in organ culture. *Lab Invest* 36(2):131-139, **1977** PMID: 839730
7. Mossman BT and Craighead JE: Organ culture of the hamster bladder epithelium. *Tissue Cult Assoc Man* 3:623-624, **1977**
8. Mossman BT: Autoradiography for determination of DNA synthesis in hamster bladder epithelium. *Tissue Cult Assoc Man* 3:663-666, **1977**
9. *Mossman BT, Heintz N, MacPherson BV, and Craighead JE: Squamous metaplasia of the tracheal epithelium in organ culture. II. Nutritional influences. *Proc Soc Exp Biol Med* 157(3):500-505, **1978** PMID: 634992
10. *Mossman BT and Craighead JE: Induction of neoplasms in hamster tracheal grafts with 3-methylcholanthrene-coated Lycra fibers. *Cancer Res* 38(11 Pt 1):3717-3722, **1978** PMID: 698931
11. *Mossman BT, Adler KB, and Craighead JE: Interaction of carbon particles with tracheal epithelium in organ culture. *Environ Res* 16(1-3):110-122, **1978** PMID: 679909
12. *Craighead JE and Mossman BT: Carcinoma induction by 3-methylcholanthrene in hamster tracheal tissue implanted in syngeneic animals. *Prog Exp Tumor Res* 24:48-60, **1979** PMID: 538263
13. Mossman BT and Craighead JE: Use of hamster tracheal organ cultures for assessing the cocarcinogenic effects of inorganic particulates on the respiratory epithelium. *Prog Exp Tumor Res* 24:37-47, **1979** PMID: 538256
14. *Mossman BT, Craighead JE, and MacPherson BV: Asbestos-induced epithelial changes in organ cultures of hamster trachea: inhibition by retinyl methyl ether. *Science* 207(4428):311-313, **1980** PMID: 7350661
15. *Craighead JE, Mossman BT, and Bradley BJ: Comparative studies on the cytotoxicity of amphibole and serpentine asbestos. *Environ Health Perspect* 34:37-46, **1980** PMID: 6993203; PMCID: PMC1568520
16. *Last JA, Kaizu T, and Mossman BT: Glycoprotein synthesis by an established cell line from hamster tracheal epithelium. *Exp Lung Res* 1(2):89-98, **1980** PMID: 7227345
17. *Mossman BT, Ezerman EB, Adler KB, and Craighead JE: Isolation and spontaneous transformation of cloned lines of hamster tracheal epithelial cells. *Cancer Res* 40(12):4403-4409, **1980** PMID: 7192176
18. Mossman BT: Use of tracheal organ cultures and grafts to explore the interactions of environmental particulates with respiratory epithelial cells. In: Topics in Environmental Pathology, (RB Hill and JA Terzian, eds.), Universities Associated for Research and Education in Pathology, Inc., Bethesda, MD, 89-, **1980**
19. Mossman BT, Adler KB, and Craighead JE: Cytotoxic and proliferative changes in tracheal organ cultures after exposure to mineral dusts. In: The In Vitro Effects of Mineral Dusts, (RC Brown, IP Gormley, M Chamberlain, R Davies, eds.) Academic Press, London, UK, 241-250, **1980**
20. *Mossman BT and Craighead JE: Mechanisms of asbestos carcinogenesis. *Environ Res* 25(2):269-280, **1981** PMID: 7023937
21. *Eastman A, Mossman BT, and Bresnick E: Formation and removal of benzo(a)pyrene adducts of DNA in hamster tracheal epithelial cells. *Cancer Res* 41(7):2605-2610, **1981** PMID: 6265063
22. *Woodworth CD, Mossman BT, and Craighead JE: Comparative effects of fibrous and nonfibrous minerals on cells and liposomes. *Environ Res* 27(1):190-205, **1982** PMID: 6279387
23. Mossman BT, Adler KB, Jean L, and Craighead JE: Mechanisms of hypersecretion in rodent tracheal explants after exposure to chrysotile asbestos. Studies using lectins. *Chest* 81(5):23S-24S, **1982**
24. *Landesman JM and Mossman BT: Induction of ornithine decarboxylase in hamster tracheal epithelial

- cells exposed to asbestos and 12-O-tetradecanoylphorbol-13 acetate. *Cancer Res* 42(9):3669-3675, **1982** PMID: 6286111
25. *Eastman A, Mossman BT, and Bresnick E: Modulation of the interaction of benzo(a)pyrene with a hamster tracheal epithelial cell line. *Carcinogenesis* 3(11):1283-1287, **1982** PMID: 6983932
26. *Craighead JE and Mossman BT: The pathogenesis of asbestos-associated diseases. *N Engl J Med* 306(24):1446-1455, **1982** PMID: 7043267
27. Mossman BT and Craighead JE: Comparative cocarcinogenic effects of crocidolite asbestos, hematite, kaolin, and carbon in implanted tracheal organ cultures. *Ann Occup Hyg* 26(1-4):553-567 **1982** PMID: 6295246
28. Mossman BT: Mechanisms of asbestos-induced carcinogenesis in hamster trachea. Proceedings of the 12th Conference on Environmental Toxicology, Report #AFAMRL-TR-81-149, Aerospace Medical Research Laboratory, 1, **1982**
29. Mossman BT and Craighead JE: Mechanisms of asbestos and nonasbestiform particles and fibers in bronchogenic carcinoma. In: Health Issues Related to Metal and Nonmetallic Mining, (WL Wagner, WN Rom, and JA Merchants, eds.), Butterworth Publishers, Boston, MA, 123-134, **1983**
30. *Mossman BT, Jean L, and Landesman JM: Studies using lectins to determine mineral interaction with cellular membranes. *Environ Health Perspect* 51:23-25, **1983** PMID: 6315363; PMCID: PMC1569312
31. *Woodworth C, Mossman BT, and Craighead JE: Interaction of asbestos with metaplastic squamous epithelium developing in organ cultures of hamster trachea. *Environ Health Perspect* 51:27-33, **1983** PMID: 6315370; PMCID: PMC1569289
32. *Mossman BT, Eastman A, Landesman JM, and Bresnick E: Effects of crocidolite and chrysotile asbestos on cellular uptake and metabolism of benzo(a)pyrene in hamster tracheal epithelial cells. *Environ Health Perspect* 51:331-335, **1983** PMID: 6315375; PMCID: PMC1569314
33. Mossman BT and Landesman JM: Importance of oxygen free radicals in asbestos-induced injury to airway epithelial cells. *Chest* 83(5 Suppl):50S-51S, **1983** PMID: 6839851
34. Mossman BT, Light W, and Wei E: Asbestos: mechanisms of toxicity and carcinogenicity in the respiratory tract. *Annu Rev Pharmacol Toxicol* 23:595-615, **1983** PMID: 6347054
35. *Wilson GL, Mossman BT, and Craighead JE: Use of pancreatic beta cells in culture to identify diabetogenic N-nitroso compounds. *In Vitro* 19:25-30, **1983** PMID: 6218070
36. *Eastman A, Mossman BT, and Bresnick E: Influence of asbestos on the uptake of benzo(a)pyrene and DNA alkylation in hamster tracheal epithelial cells. *Cancer Res* 43(3):1251-1255, **1983** PMID: 6297722
37. *Woodworth CD, Mossman BT, and Craighead JE: Squamous metaplasia of the respiratory tract. Possible pathogenic role in asbestos-associated bronchogenic carcinoma. *Lab Invest* 48:578-584, **1983** PMID: 6843088
38. *Woodworth CD, Mossman BT, and Craighead JE: Induction of squamous metaplasia in organ cultures of hamster trachea by naturally occurring and synthetic fibers. *Cancer Res* 43(10):4906-4912, **1983** PMID: 6883341
39. *Mossman BT: *In vitro* approaches for determining mechanisms of toxicity and carcinogenicity by asbestos in the gastrointestinal and respiratory tracts. *Environ Health Perspect* 53:155-161, **1983** PMID: 6363051; PMCID: PMC1569089
40. *Craighead JE, Adler KB, Butler GB, Emerson RJ, Mossman BT, and Woodworth CD: Health effects of Mount St. Helens volcanic dust. *Lab Invest* 48:5-12, **1983** PMID: 6823090
41. *Mossman BT, Eastman A, and Bresnick E: Asbestos and benzo(a)pyrene act synergistically to induce squamous metaplasia and incorporation of [³H]thymidine in hamster tracheal epithelium. *Carcinogenesis* 5(11):1401-1404, **1984** PMID: 6488462
42. *Adler KB, Mossman BT, Butler GB, Jean LM, and Craighead JE: Interaction of Mount St. Helens' volcanic ash with cells of the respiratory epithelium. *Environ Res* 35(2):346-361, **1984** PMID: 6510386
43. *Wilson GL, Patton NJ, McCord JM, Mullins DW, and Mossman BT: Mechanisms of streptozotocin- and Jeanalloxan-induced damage in rat B cells. *Diabetologia* 27(6):587-591, **1984** PMID: 6241574
44. *Bernacki RJ, Wilson GL, Mossman BT, Angelino N, Kanter PM, and Korytnyk W: The therapeutic and diabetogenic potential of two newly synthesized nitrosoureido sugars. *Cancer Res* 45(2):695-702, **1985** PMID: 3881170
45. Mossman BT and Marsh JP: Mechanisms of toxic injury by asbestos fibers: role of oxygen-free radicals.

- In: *In Vitro Effects of Mineral Dusts*, 3rd International Workshop, (EE Beck and J Bignon, eds.), NATO ASI Series, Springer-Verlag, Berlin, Germany 66-74, **1985**
46. Fisher GL, Mossman BT, McNeill K, Marsh JP, McFarland AR and Hart RW: Investigations into the mechanisms of asbestos toxicity. In: *In Vitro Effects of Mineral Dusts*, 3rd International Workshop, (EE Beck and J Bignon, eds.), NATO ASI Series, Springer-Verlag, Berlin, Germany, 31-38, **1985**
 47. Marsh JP, Jean L, and Mossman BT: Asbestos and fibrous glass induce biosynthesis of polyamines in tracheobronchial epithelial cells *in vitro*. In: *In Vitro Effects of Mineral Dusts*, 3rd International Workshop, (EE Beck and J Bignon, eds.), NATO ASI Series, Springer-Verlag, Berlin, Germany, 305-311, **1985**
 48. Mossman BT, Cameron GS, and Yotti LP: Cocarcinogenic and tumor promoting properties of asbestos and other minerals in tracheobronchial epithelium. In: *Cancer: A Comprehensive Survey* (Cancer of the Respiratory Tract, Predisposing Factors, Vol. 8), (MJ Mass, DG Kaufman, JM Siegfried, VE Stede, S Nesnow, eds.), Raven Press, New York, NY, 217-238, **1985**
 49. Mossman BT, Eastman A, Landesman JM, Bresnick E, and Craighead JE: Interactions of asbestos and polycyclic aromatic hydrocarbons (PAH) in carcinogenesis of the respiratory tract. In: *Occupational Lung Disease*, (JBL Gee, WK Morgan, and SM Brooks, eds.), Raven Press, New York, NY, 171-173, **1985**
 50. *Mossman BT, Wilson GL, and Craighead JE: Chlorozocin. A diabetogenic analogue of streptozocin with dissimilar mechanisms of action on pancreatic beta cells. *Diabetes* 34(6):602-610, **1985** PMID: 3159609
 51. Mossman BT and Eastman A: Carcinogenesis and lung cancer. In: *Lung Carcinomas* (EM McDowell, vol. ed.), In Series: *Current Problems in Tumor Pathology*, (J Azzopardi and N Wright, series eds.), Churchill Livingstone, London, UK, 129-161, **1986**
 52. Mossman BT: Mechanisms of chemical and physical carcinogenesis in cultured hamster and human tracheobronchial epithelium. In: *In Vitro Models of Respiratory Epithelium*, (LJ Schiff, ed.), CRC Press, Inc., Boca Raton, FL, 161-182, **1986**
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 55. *Mossman BT, Ireland CM, Filipak M, LeDoux S, and Wilson GL: Comparative interactions of streptozotocin and chlorozotocin with DNA of an insulin-secreting cell line (RINr). *Diabetologia* 29(3):186-191, **1986** PMID: 2938999
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 57. Finch GL, Hayes TL, Mossman BT, Chang MJW, and Fisher GL: SEM of tracheal respiratory epithelium exposed *in vitro* to Ni₃S₂. In: *Microbeam Analysis - 1986*, (AD Romig, Jr. and WF Chambers, eds.) San Francisco Press, San Francisco, CA, 591-593, **1986**
 58. *Hansen K and Mossman BT: Generation of superoxide (O₂⁻) from alveolar macrophages exposed to asbestiform and nonfibrous particles. *Cancer Res* 47(6):1681-1686, **1987** PMID: 3028612
 59. *Shatos MA, Doherty JM, Marsh JP, and Mossman BT: Prevention of asbestos-induced cell death in rat lung fibroblasts and alveolar macrophages by scavengers of active oxygen species. *Environ Res* 44(1):103-116, **1987** PMID: 3115771
 60. Mossman BT and Craighead JE: Mechanisms of asbestos associated bronchogenic carcinoma. In: *Asbestos-Related Malignancy*, (K Antman and J Aisner, eds.), Grune and Stratton, New York, NY, 137-150, **1987**
 61. Craighead JE and Mossman BT: Pathogenesis of mesothelioma: In: *Asbestos-Related Malignancy*, (K Antman and J Aisner, eds.), Grune and Stratton, New York, NY, 151-162, **1987**
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Books/Series Editor

1. BT Mossman and RO Begin, eds.: Effects of Mineral Dusts on Cells, NATO ASI Series H: Cell Biology, Springer-Verlag, Berlin, Germany, pp.1-470, **1989**
2. GD Guthrie Jr. and BT Mossman, eds.: Health Effects of Mineral Dusts, Reviews in Mineralogy, Vol. 28 (Series Editor: Paul H. Ribbe), Mineralogical Society of America, Washington, DC, pp. 1-584, **1993**
3. BT Mossman (Guest Editor): Forum on "Signal transduction by oxidants: Look who's talking". *Free Radic Biol Med* 28(9):1315-1316, **2000** PMID: 10924850
4. DJ Taatjes and BT Mossman, eds.: Cell Imaging Techniques: Methods and Protocols (Methods in Molecular Biology, Vol. 319), Humana Press, Totowa, NJ, pp. 1-490, **2006**

Research Support

NIH NIOSH (09/01/1978 - 08/31/1982) "Carcinogenic Mechanisms of Asbestos", Total \$397,899; PI - 50% FTE
 NIH NIAM (07/01/1979 - 06/30/1982) "Establishment of Insulin-secreting Cell Lines", Total \$101,980; PI - 30% FTE (Young Investigator Grant)
 NIH NCI (07/01/1982 - 08/30/1985) "Role of Minerals as Co-factors in Bronchogenic Carcinoma", Total \$350,132, first year \$108,444; PI - 30% FTE
 Parker B. Francis Foundation (07/01/1982 - 06/30/1985) Post-doctoral fellowship - Maria A. Shatos, Total \$63,174, first year \$20,566; Program Director
 ADA (08/01/1982 - 07/30/1984) "Diabetogenic Chemicals: Mechanisms of Tropism for and Damage to Pancreatic Beta Cells", Total \$49,877, first year \$24,607; PI - 15% FTE (returned 02/01/1983 because of over commitments)

American Cancer Society, Institutional Research Award (09/01/1982 - 08/31/1983) "Comparative Interactions of Methylnitrosourea with the DNA of Pancreatic Beta Cells and Fibroblasts", Total \$7,500; PI - 5% FTE

American Cancer Society (01/01/1983 - 12/31/1985) "Fiber-cell Interaction in Bronchogenic Carcinoma", Total \$332,280, first year \$98,444; PI - 30% FTE

NIH NIEHS (02/01/1983 - 01/31/1986) "N-nitroso Compounds: Mechanisms of Damage to Beta Cells", Total \$327,306, first year \$96,283; PI - 20% FTE

NIH NCI (09/01/1985 - 08/30/1988) "Oxygen Radicals in Mineral Damage/Tumor Promotion", Total \$347,508, first year \$106,580; PI - 30% FTE

NIH NIEHS (02/01/1986 - 01/31/1989) "Preventive Approaches to Mineral-induced Fibrosis", Total \$328,339, first year \$104,355; PI - 50% FTE

NHLBI (12/01/1986 - 11/30/1991) Pulmonary SCOR - Occupational and Immunologic Lung Disease, Director Project 05, "Preventive approaches to asbestosis", ADC \$62,656; 15% FTE

NATO Advanced Research Workshop grant (07/01/1988 - 12/30/1988) "Effects of Mineral Dusts on Cells", Total \$22,500

NIH NHLBI/NIEHS/NCI (09/01/1988 - 08/31/1989) Conference grant, "Workshop on Effects of Mineral Dusts on Cells", Total \$28,000

American Cancer Society (06/01/1989 - 06/30/1990) Fellowship for Susan Edmondson, Total \$1,200

Howard Hughes Helix Award (01/01/1990 - 12/31/1990) Undergraduate support for Kaaren Haldeman, TDC \$800

EPA (09/01/1991 - 12/31/1994) "Lung Defense Mechanisms after Occupational and Environmental Exposure to Asbestos", first year \$150,000, TDC \$450,422; PI - 15% FTE

NIH NHLBI (04/01/1993 - 03/30/1997) "Molecular Biology of Lung Antioxidant Enzyme Regulation", ADC \$168,887; PI - 40% FTE

NIH (09/01/1993 - 08/31/1998) "Mechanisms of Cell Replication in Asbestos Cancers", ADC \$138,570; PI - 38% FTE

NIH NIEHS (02/01/1994 - 01/31/1999) "Asbestos-Induced Oxidative DNA Damage and Repair", ADC \$44,239; Subcontract - Bennett Van Houten PI

NIH NIOSH (10/01/1994 - 09/30/1997) "Stress Genes as Biomarkers of Mineral Dust Exposure", Advisor to Dr. Cynthia R. Timblin for Special Emphasis Career Development Award, ADC \$50,000

Parker B Francis Foundation (07/01/1995 - 06/30/1998) "Molecular Pathways of Proliferation and Inflammation Activated in Lung Epithelial Cells by Reactive Oxygen and Nitrogen Species", ADC \$29,875; Yvonne Janssen PI

NIH (08/01/1996 - 07/31/2000) "The Nature of Lung Antioxidant Defense Mechanisms", ADC \$25,505; Subcontract - Ye-Shih Ho, PI

NIH (09/30/1997 - 09/29/2001) "EGFR Signaling Pathways by Particulates in Lung Disease", ADC \$183,546; PI - 30% FTE

NIH (06/01/1998 - 05/30/2001) "Molecular Signaling by Oxidant Stress in Lung Epithelium", ADC \$185,728; PI - 35% FTE

NIH (08/15/1998 - 07/31/2002) "Asbestos and NO₂ in Environmental Lung Disease", ADC \$189,648; Nicholas H. Heintz PI

NIH (11/19/1998 - 11/23/1998), 1998 Oxygen Society Meeting Conference Grant, TDC \$39,928

NHLBI (09/01/2005 - 08/31/2006), 8th International Meeting on "Mechanisms of Action of Inhaled Fibers, Particles and Nanoparticles", ADC \$30,000; PI - 0% FTE

NIH P01 HL67004/01-05 (06/01/2001 - 04/30/2006; NCE - 04/30/2007) "Signaling in Epithelial Injury, Proliferation and Fibrosis", Total project ADC: \$1,049,247; PD: Project 1, "MAPK Signaling in Injury, Proliferation & Fibrosis", ADC: \$167,351; PL - 25% FTE: Project 3, "Protein Kinase C and MAPK in Epithelial Responses", ADC: \$191,711; Co-I - 15% FTE: Core A, "Administrative Core", ADC: \$85,513; CL - 10% FTE

NIH NIEHS R01 ES10638-01 (08/08/2003 - 07/31/2007) "Molecular Regulation of Transcriptional Competence by Metals", ADC \$86,915; Aaron Barchowsky PI (University of Pittsburgh)

NCI K01 CA104159 (05/01/2004 - 04/30/2008) "Role of Fra-1 in Mesothelioma", ADC: \$129,415 Maria E. Ramos-Nino PI

MARF (01/01/2007 - 12/31/2008; NCE - 12/31/2009) "Nanoporous Spheres for Chemotherapeutic Drug Delivery in Mesothelioma Patients", ADC: \$50,000; PI - 5% FTE

NIH NCI R01 CA106567 (04/01/2005 - 03/31/2010) "Role of Inflammatory Mediators in Asbestos and Simian Virus (SV40) Carcinogenesis", ADC: \$19,750 (Subcontract); Michele Carbone, PD (University of Hawaii), Co-I - 3% FTE

NIH 1R41 CA12615501 (09/27/2007 - 07/31/2010) "Improving the Transfer of ERK siRNA Constructs Using Nanoporous Silica", ADC: \$94,503; Christopher C. Landry PI, Co-I - 2% FTE

Eurotalc/Industrial Minerals Association (11/01/2005 - 10/31/2010) "Comparative Effects of Nonasbestiform Talc and Asbestos on Gene Profiles and Proliferation/Cell Death in Human Pleural Mesothelial and Ovarian Epithelial Cells *in Vitro*", TDC: \$90,000, PI (This project did not result in any salary support for the PI)

NIH NIEHS RC1 ES018053-01 (10/01/2009 - 07/31/2011) "Mechanisms for Cardiovascular Effects of Air Pollutants: Effect of Age and Sex", ADC: \$332,223; Naomi K. Fukagawa PI, Co-I - 5% FTE

NCI P01 CA11407 (08/01/2006 - 08/31/2011) "Pathogenesis of Mesothelioma"; Project 2 Leader, "ERK Pathways in Pathogenesis and Chemoresistance of Mesothelioma", ADC: \$206,512 (Subcontract); Michele Carbone, PD (University of Hawaii), Co-I - 25% FTE

NIH/NIEHS T32 ES007122 (07/01/1982 - 06/30/2013) "Environmental Pathology Training Grant" (Director), TDC \$2,500,000 for a five-year period. The major goal of this project is to provide graduate training in environmental pathology. Six pre-doctoral and three post-doctoral positions are funded annually. PI - 10% FTE

Research (2010-2016) on silica and silicosis was supported by an unrestricted grant from the Weijerhorst Foundation in collaboration with researchers at the University of Maastricht, The Netherlands.

NIEHS (2016) R13 Conference grant for support of junior/underrepresented minorities for attendance at the 11th International Particles/Toxicology Conference"; Singapore, Co-PI (no salary support) Gunter Oberdorster, PI.

DOD (09/01/2014-8/31/2016) "Exosomes in Development and Therapy of Malignant Mesothelioma", Total \$300,000; Co PI- 4% FTE (1 year non-funded extension- 8/31/2017).